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EDITORIAL

This issue of the Medical Journal represents Number 3 of Volume XXIII and is at present being distributed to six years, two premedical and four medical.

Due to the predominance of clinical articles, the Journal may seem of little interest to those students in the preclinical classes. They are distributed to them, however, in the hope that they will be kept and found to be of value at a later date.

The continued success of the Journal depends to a large extent on the contributions of undergraduates as well as those of graduates and members of the staff. There are two types of articles which are particularly useful to undergraduates. One is a discussion of symptoms of a condition which would lead to the making of a provisional diagnosis; the other is a review of recent literature which would render a clear organized picture of a disease.

We shall be very glad to receive undergraduate articles. May we suggest that subjects chosen apply to fairly common maladies and that these be discussed from the standpoint of a practising physician.

To Peter Allen and his staff may we express our appreciation for their fine work during the past year.

Those wishing subscriptions or back copies are advised to contact Mr. O. E. Laxdal, Circulation Manager, Room 107 Anatomy Building.

THE RH FACTOR AND ERYTHROBLASTOSIS FOETALIS

R. SLATER

This paper constitutes a simplified summary of the latest literature concerning Rh factor. It is designed to give the medical student an introduction to and a working knowledge of the subject.

I. History

To Landsteiner goes the credit of discovering the individual differences in human blood which underlie the four groups: O, A, B, AB. Later Landsteiner, working with Levine brought to light three more blood agglutinogens: M, N and P. In 1940 Landsteiner and Wiener, using the serum of a rabbit immunized with erythrocytes from a rhesus monkey, discovered an agglutinin which agglutinated 85% of a group of white individuals in New York, irrespective of their blood group. They designated the new agglutinogen, in conformance with the origin of the serum, as Rh. The Rh factor is a specific agglutinogen associated with the red cells, existing as either a positive or a negative factor. If the red cells contain the Rh. agglutinogen, they are designated Rh-positive (Rh+), and if the factor is not present they are designated Rh-negative (Rh–).

II. Incidence

This specific antigenic factor is present in the red cells of 85-87% of the white population of the Americas and England, leaving 13-15% Rh–. The Rh factor is found in 90-95% of negroes and approximately 99% of Chinese.

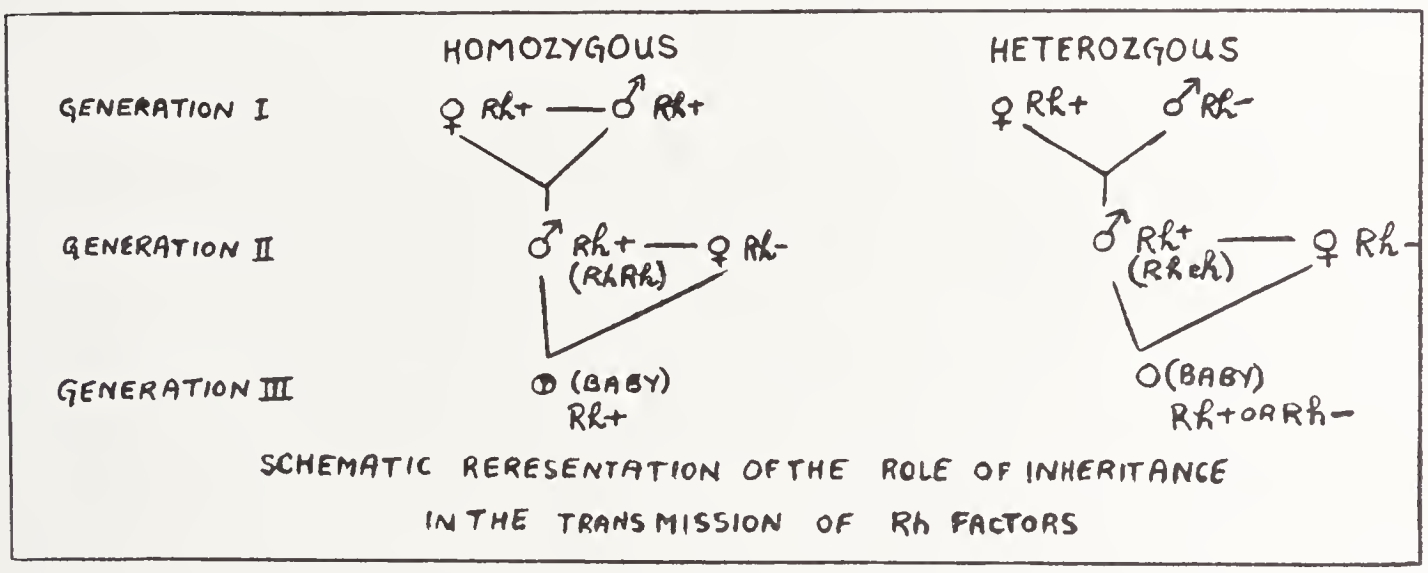
III. Relation to Inheritance

The inherited characteristics of animals and plants are determined by submicroscopic units called genes. These genes are arranged in serial fashion in rod-like structures which are visible under suitable conditions in the nuclei of reproductive and other cells. The rods are called chromosomes. All the genes in any one chromosome are transmitted together from parent to offspring, and the number of gene groups in heredity is observed to correspond to the number of chromosomes in the reproductive cells of the species. This number varies from species to species.

In the fertilized gamete and in the adult organism the cell nuclei are observed to contain twice the number of chromosomes found in the reproductive cell; in fact, they contain two of each sort of chromosome, one member of each pair from the father and one from the mother. The respective members of a pair are very much alike, sometimes identical, in the genes they contain, and in the order in which the genes are arranged, and any difference is a reflection of a difference between the genetic constitutions of the mother and the father. For any particular gene, or for other genes which can substitute for it in inheritance, there will be available in the nucleus of the fertilized gamete just two locations, one at some point of a certain chromosome, and another at the corresponding point of the other member of the chromosome pair.

As long as only one kind of gene is available to fill these locations, all fertilized gametes will be alike in regard to this particular type of gene, and all offspring of every mating will be identical in respect to the characters determined by it. The situation becomes interesting when there is available more than one kind of gene which can occupy this particular location on the chromosome. There is a chance for parents and offspring to differ in this characteristic.

Based on the above explanation of Boyd the inheritance of the serological characteristics may be outlined. The Rh factor will be used in the example. At a certain location of a certain chromosome there may occur a gene which may be designated Rh. Since men and women do not choose their mates on the basis of blood types, the random mating which results gives three sorts of combinations of chromosomes, a pair with Rh on both, a pair with neither on both (absence of Rh factor is designated rh, therefore rh on both), a pair of which one bears Rh and one bears rh. In this explanation, other genes which may be present are ignored as we are concerned only with Rh. The genetic constitution of a person is called his genotype and the possible genotypes according to the above are RhRh, rhrh, and Rhrh. The resultant, observable, physical constitution is called the phenotype. The phenotypes corresponding to the respective genotypes would be Rh+, Rh– and Rh+.



SCHEMATIC RERESENTATION OF THE ROLE OF INHERITANCE IN THE TRANSMISSION OF Rh FACTORS

In this subject we are concerned for the main part in Rh– mothers and Rh+ fathers. If the father's parents are both Rh+, it stands to reason that he will be Rh+ and that his reproductive cell will carry chromosomes bearing two Rh genes (RhRh). Considering the mother to be Rh–, the fetus will be Rh+. Because his chromosomes carry two Rh genes, the father is termed "homozygous" and cannot bear anything but Rh+ children. However if the father's parents are mixed, one Rh+ and the other Rh–, he may or may not be Rh+, and his genes are certain to be dissimilar, one Rh+ and one Rh– (Rhrh). Again assuming the father's wife to be Rh–, his children have an equal chance of being Rh+ or Rh–. The father, because his Rh genes are dissimilar, is referred to in this instance as "heterozygous".

IV. Subtypes of Rh Factor

So far we have discussed Rh as a single agglutinogen inheritably linked to the red blood cell. Unfortunately the explanation does not stop here because it has

been proven that the Rh factor is not a single entity but is actually any one of series of subtypes. Wiener's new nomenclature defines the principal series of allelic genes concerned in the Rh factor as rh, Rh_0, Rh′, Rh″, Rh_1 and Rh_2. Of these, rh is the Rh– gene.

With so many genes involved, it is readily understood that mating will produce combinations and permutations of these different genes to such proportions that only a full-time specialist can retain a working knowledge of them. It is more reasonable for the student to refer simply to the main consideration, either the presence or absence of the factor. The above subtypes are referred to as being allelic or allelomorphs of the Rh factor, because any one of the six Rh subtypes, but not more than one, can occupy the location of the Rh gene on the chromosome.

The specific anti Rh agglutinins induced by the correspondingly specific Rh agglutinogen subtypes are used in typing individuals. The three antiserums anti Rh_0, anti Rh′ and anti Rh″ plus the anti Hr serum are used also in determining if a parent is homozygous or heterozygous. Therefore it is possible to forecast whether all the children of an Rh+ father will be Rh+ or just some of them, depending upon whether he is homozygous or heterozygous.

The Hr factor is another newly discovered subtype about which little is definitely known, although it has been used in typing as stated above.

V. Mechanics of Action of the Rh Factor

A—*Sensitization and Isoimmunization:*

1. In Pregnancy:—Since the Rh factor is an agglutinogen it has the antigenic effect of being able to sensitize an individual who does not bear this factor. Thus if Rh+ cells are introduced into the blood stream of an Rh– individual, this foreign agglutinogen stimulates the blood to produce a specific antibody known as the anti Rh agglutinin, which will then upon subsequent stimulation react in antagonism to the agglutinogen and an incompatibility response of the individual occurs. The anti Rh agglutinin is a product of the serum and from it the standard anti Rh sera are derived for laboratory tests.

When a homozygous or heterozygous father transmits the Rh factor to a fetus which is being produced in an Rh– mother, it can be readily understood that "something" must happen because the blood of the Rh+ fetus is incompatible with that of the Rh– mother. It is possible for the agglutinogen of the Rh+ fetus to pass the placental barrier and enter the maternal circulation thus initiating the production of Rh antibody in the mother's serum. The antibody in turn migrates back through the placenta to the fetal circulation, reacts with the Rh agglutinogen and causes erythroblastosis fetalis to occur. The seriousness of the intrafetal hemolysis is dependent upon the titre strength of antibody which is passed to the fetus from the mother.

The obvious question which one would ask is, that since the agglutinogen is attached to the red cells, and the fetal and maternal circulation do not interchange, how does the agglutinogen reach the maternal circulation. It is thought that small numbers of red cells in one form or another pass from fetal to maternal circulation

in every normal pregnancy. This would induce isoimmunization if the cells were Rh+ and the mother's Rh–. However isoimmunization occurs in only a small percentage of Rh– women with Rh+ husbands therefore it is with confidence that the physician can reassure those Rh– women who have become alarmed by newspaper and magazine accounts. She should be instructed that most of them may have two or more normal infants before they become sufficiently immunized to produce erythroblastotic infants.

The continuous transudation of Rh agglutinin (Rh antibody) from the mother to the fetus via the placenta produces continuous destruction of the fetal red cells. Thus, it may be readily understood why, in a fetus suffering under this handicap, there occurs persistent extra-medullary hematopoiesis in response to the excessive hemolysis. This is characterized by the presence of numerous nucleated red cells in the fetal circulation. These immature red cells explain the inability of the fetus to supply adequate mature red cells due to the Rh incompatibility.

At birth there is a certain amount of the mother's Rh agglutinin in the fetal circulation which continues to produce hemolysis. However since augmentation of this factor is removed at birth, it gradually decreases in amount. Thus if the baby's well-being can be maintained during this short period by repeated transfusions of Rh– blood (i.e. until the Rh agglutinins have been neutralized to non-existency) the child may be expected to carry on as a normal infant.

It has recently been discovered that the milk of a sensitized (isoimmunized) Rh– mother carries the anti Rh agglutinin, therefore it is reasonable to assume that the hemolytic reaction will continue in the infant if it is breast fed, despite therapeutic efforts at transfusion.

In testing pregnant females, the presence of anti Rh agglutinins, which is direct proof of immunization, can be demonstrated in only 50% of Rh– mothers, even if tested soon after delivery. This difficulty has recently been explained on the basis that many Rh– mothers of erythroblastotic infants have anti Rh antibodies which specifically unite with and coat the surface of the Rh+ cells without inducing the visible effect of agglutination. In other words the antibody is incomplete because only the first phase of the reaction (i.e. specific union; second phase—permeation and hemolysis) occurs. In the laboratory tests the specifically coated Rh+ cells are incapable of reacting with the potent anti Rh agglutinins and thus the test is unsuccessful when it really should be indicatively positive. This incomplete antibody has been termed the "blocking" antibody. In vivo the specific reaction certainly goes to completion so that the end result is hemolysis. In other words, clinically one cannot differentiate erythroblastotic infants of mothers who have complete Rh agglutinins from those whose mothers have incomplete or blocking agglutinins. By the same token, both groups of mothers are subject to severe and even fatal hemolytic reactions if they are transfused with Rh+ blood. The problem evolves about the difficulty in detecting by laboratory methods those isoimmunized Rh– mothers who have the blocking antibody which won't react with standard anti Rh serum.

It is important to know that Rh+ blood can induce immunization in an Rh–

individual within seven days assuming the stimulus is adequate i.e. as in transfusion. However in pregnancies, the stimulus of fetal Rh+ cells leaking into maternal Rh– blood is so small, that usually one and sometimes two normal pregnancies may be effected before the anti Rh agglutinin in the mother's serum becomes of sufficiently high titre to make the symptoms of erythroblastosis fetalis manifest. Once initiated however, the prognosis becomes progressively worse with each succeeding pregnancy, so long as the mother continues to bear Rh+ children.

2. In the Non-Pregnant State:—Transfusing an Rh– man or woman with Rh+ blood will produce anti Rh agglutinins as rapidly as seven days as mentioned above. Then on the second and subsequent transfusions of Rh+ blood, the individual experiences hemolytic reactions. If this individual be a woman and she develops a subsequent Rh+ pregnancy, the already present highly titred anti Rh agglutinin in her serum is sure to induce erythroblastosis fetalis if the fetus is Rh+. This would account for those cases of severe erythroblastosis occurring in the first pregnancy. Again, Rh– women who have, in the course of pregnancy, developed anti Rh agglutinins may experience serious transfusion reactions dating from the *first* transfusion by receiving Rh+ blood.

VI. Clinical Effects of Rh Incompatibility

A—*Transfusion Reactions:*

These occur in any blood incompatibility and are not limited to the Rh factor. The clinical effects are due to hemolysis of red cells and resultant shock plus intravascular agglutination. Reactions may consist of nothing more than a mild fever of about 100°F with no objective symptoms. Fortunately the majority of transfusion reactions are not serious, being characterized by fever and chills and possibly hemoglobinuria and jaundice. Severe reactions due to gross incompatibility however are not necessarily fatal even when large amounts of blood are transfused. The symptoms include violent pains in the back, chills, respiratory embarrassment, circulatory collapse, hematuria, hemoglobinuria, jaundice, urticaria and symptoms due to small hemorrhages or emboli in the brain, mesentery, endocardium and gastrointestinal mucosa. The terminal stages of those who survive the immediate effects are characterized by renal failure.

B—*Erythroblastosis Fetalis:*

Macklin has defined erythroblastosis fetalis as a condition in which the blood of the fetus exhibits immature cells of the erythrocytic type which are not normal as to either type or quantity for the stage of development of the fetus. These cells are present because of the hemolysis and agglutination which is due directly to the antigen-antibody reaction within the fetal circulation, and is accompanied by an accumulation of iron in the fetal liver and persistent extramedullary hematopoiesis.

An average clinical picture may be portrayed for illustration. Jaundice appears soon after birth with hepatomegaly, splenomegaly and symptoms such as somnolence, listlessness and flaccidity, or muscular irritability and twitching, opistho-

tonus and occasional convulsions, vomiting, diarrhea, petechiae, ecchymoses, bleeding from mucous surfaces, increased bleeding and coagulation time, edema, cyanosis and respiratory difficulty. The infants appear strong and vigorous at birth however symptoms appear soon and death may occur in a few hours or days, but sometimes not until the second or third week.

Erythroblastosis fetalis may be classified into three types depending upon its severity. The first type, known as Congenital Anemia, is the mildest form and is manifest only as a mild anemia which gradually becomes more severe. The second type, known as Icterus Gravis, is moderately severe and is manifest by a more profound anemia plus hemorrhagic tendencies and jaundice. The third type and most severe is Hydrops Fetalis in which great damage has been done. Universal edema exists and the infant cannot survive.

The same mother can give birth to infants suffering from any of the above three forms of erythroblastosis fetalis. The usual sequence is an increase in the severity of the disease in successive pregnancies; mild at first and progressively becoming more severe. Davidson states that there are four factors determining the severity of erythroblastosis fetalis: (1) the age of the fetus when the agglutinins begin to act; (2) the length of time the agglutinins act; (3) the strength of the anti Rh agglutinins i.e. titre in the mother may or may not be a measure; (4) permeability of the placenta varies in different women, and in the same women at different times during the pregnancy. The Rh agglutinogen develops in the fetal blood cells about the eighth or tenth week of embryonic life, therefore if erythroblastosis is going to occur it usually has an early onset. The worst form of the disease occurs in a woman who has been highly sensitized (to a high anti Rh agglutinin titre,) by a previous Rh transfusion, in which event the fetus probably dies about the eighth or ninth month in utero.

An interesting hypothesis recently advanced is the relationship of erythroblastosis fetalis of kernicterus. Kernicterus, which is a bile stained degeneration of the cranial nuclear centres, is found primarily in erythroblastotic infants. This interesting feature was brought to light when Yannet observed that certain infants recovering from icterus gravis subsequently exhibited a central nervous system injury such as mental deficiency, extra-pyramidal spasticity and athetosis. Yannet suggests that certain cases of imbecility and idiocy now classified as of unknown etiology may arise as a result of Rh isoimmunization in the parent.

VII—Incidence of Erythroblastosis Fetalis

It is with thankfulness that we may note that erythroblastosis fetalis affects the offspring of only one in every two hundred to four hundred births. Potter states that only 12% of all marriages are between Rh– females and Rh+ males and it is to this group that we naturally turn our interest and attention. Theoretically then, erythroblastosis fetalis is possible in 12% of marriages however it only actually occurs in 0.05%, i.e. one case in every two hundred pregnancies which includes Rh+ and Rh– mothers. Javert found that 92% of mothers of erythroblastostic

infants are multiparas and that the incidence of erythroblastosis varies with parity. For example if erythroblastosis appears in the second or subsequent child, about 50% of the subsequent children may have it. However if it appears in the first-born in all likelihood 100% of any subsequent children will succumb, the condition appearing progressively worse in each child.

VIII—Treatment of Erythroblastosis Fetalis

Treatment depends entirely upon the condition of the infant at the time of delivery and subsequently:

1) if it be apnoeic and cyanotic, intratracheal or intranasal oxygen is administered;
2) a red cell count must be done immediately and if it is 3.5 or more, transfusion is unnecessary;
3) the red cell count should be repeated daily and if it does not drop in the succeeding five days, the prognosis is good;
4) if a transfusion is necessayry, Rh- blood is most satisfactory. By repeated transfusions the infant can live until the hemolytic agglutinins have been neutralized. An Rh- transfusion is desirable, despite the fact that the baby is R+, because it has been found that following transfusion, the Rh- cells survive upwards of ninety days, whilst Rh+ cells are hemolyzed within a few days of transfusion.
5) Usually 50--60 ccs. of blood is required for each transfusion and two to six transfusions may be necessary.

IX—Prophylaxis

When a pregnant woman is discovered Rh-, her blood should be tested for Rh antibodies. Serial dilutions of her serum are tested against the cells which she agglutinates and by standardizing against a standard anti Rh serum, the titre of agglutinin in her blood may be determined.

Tires of the agglutinin level should be made every six weeks for the first seven months and every four weeks thereafter. As the titre rises, the danger of the occurrence of erythroblastosis fetalis rises. The titre may suddenly drop due to the appearance of a blocking antibody, which as was explained above interferes with the agglutination of Rh+ cells by the standard anti Rh sera but which does not interfere with the intrauterine progress of the disease. The presence of the blocking antibody lends an especially poorly prognosis, its presence being very serious as it cannot be determined quantitatively.

The length of exposure of the fetus to these agglutinating and blocking antibodies may be lessened (and therefore the damage done also lessened) by premature delivery by cesarean section. This is best done when the agglutinin titre falls, before the blocking antibody titre starts to rise. The infant may then be tided over by repeated transfusions.

Also of note is the fact that it is now possible to discover whether Rh+ fathers are homozygous or heterozygous. If the mother has had a previous erythroblastotic infant and the father is homozygous Rh+, she should be advised against having

further pregnancies. However if she has been previously isoimmunized (by pregnancy or transfusion) and her husband is heterozygous, she has about a fifty-fifty chance of bearing a normal child. As yet, there have been no methods discovered to prevent erythroblastosis fetalis other than prophylaxis.

In closing it may be well to remark that, according to statistics, some 8% of erythroblastosis fetalis occurs in Rh+ mothers and this might be accounted for by the fact that a rare intra Rh+ group (clashing of subtypes) hemolytic reaction has occurred.

X—Laboratory Detection of Rh Factor

A suspension of red blood cells is placed in 0.01 cc. of a 2% isotonic solution of sodium chloride with 0.02 cc. of anti Rh serum in a test tube for one hour in a water bath at 37°C. Fresh blood must always be used. A positive reaction is noted macroscopically when the agglutinated sediment in the bottom of the tube has a rough appearance. Agitation of the tube causes clumping of the cells and this must be checked microscopically. A negative reaction is evidenced by a smooth structureless sediment in the bottom of the test tube which does not clump on agitation.

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THYROTOXICOSIS

Thyrotoxicosis is a condition resulting from some disturbance in the thyroid gland characterized by an accelerated state of tissue oxidation and hyperactivity of the autonomic nervous system. Literally the term means a condition of poisoning by the thyroid gland probably due to an excess of thyroid secretion into the circulation. Clinical illustration of this condition may be found in exophthalmic goitre or toxic adenoma, these two being most commonly seen of all diseases showing thyrotoxicosis. Since the whole etiological background leading up to thyrotoxicosis is still not entirely understood it is the purpose of this article to deal with the more practical aspect of the subject. The content of this article will be discussed under the general headings of:

1. Clinical Features.
II. Treatment.
III. Prognosis.

I Clinical Features

A. Signs and Symptoms

The patient suffering from thyrotoxicosis presents a multiplicity of subjective sensations and objective signs which are quite characteristic of the condition. These may be grouped together as the following:

1. Nervous Manifestations—the patient may show extreme restlessness, emotional instability in the form of weeping spells without adequate cause, nervousness and irritability. These symptoms are present to a greater degree in cases of exophthalmic goitre than in toxic adenomas.

2. Goitre—the thyroid gland is usually palpable, being diffusely and moderately enlarged in exophthalmic goitre and nodular in cases of toxic adenomas. Even in cases where a portion of the gland lies substernally the upper limits of its margin usually may be made out upon careful palpation. Increased firmness and the presence of a systolic bruit over one or both superior poles are points of importance to record.

3. Tremor—these are fine rapid shaking of the hands as compared to the slow pill-rolling tremor of Parkinson's disease. This sign may best be demonstrated by placing the outstretched hand over a printed sheet and observing the fine flickering shadow of the hand upon the sheet.

4. Cardiac Manifestations—tachycardia, palpitation, shortness of breath and forceful beating of the heart are the usual findings. Auricular fibrillation present in transient or prolonged attacks may be observed in a few, but auricular flutter is rarely detected in the thyrotoxic patient. Especially in hearts previously damaged by rheumatic heart disease or arteriosclerosis, the symptoms of fibrillation and cardiac decompensation may be evident, and these patients are termed thyrocardiacs. Some believe the dyspnoea in thyrotoxicosis is due to the specific action of hormone on the cardiac muscle since the musculature of the skeletal system is likewise weak-

ened. The pulse pressure is usually high with a high systolic reading and a relatively normal diastolic pressure.

5. Ocular signs—the prominence of the eyeball is present only in 60-70% of exophthalmic goitres and is not particularly evident in toxic adenoma. The mechanism of production of the exophthalmos is not entirely known although we can surmise that probably a hormone from the pituitary which also stimulate the thyroid is responsible. Exophthalmos does not regress in all cases where the thyrotoxicosis is controlled. The exophthalmos may be the first sign of thyrotoxicosis and may precede the rise in B.M.R. by as much as 6 months. Other ocular signs which may be found are lid-lag, poor convergence and lack of winking.

6. Loss of weight—despite the ravenous appetite of the patient and the high caloric intake the loss of weight may continue. This is due to the high B.M.R. in the thyrotoxic patient and the normal caloric intake may be doubled before the patient can maintain a steady weight.

7. Gastrointestinal symptoms—in about 1/3 of all these cases diarrhea is a noticeable factor but other forms of gastrointestinal distress may be manifested such as nausea or vomiting. When the latter symptoms appear they are thought to indicate the severity of the condition and therefore treatment must be started immediately. Symptoms may persist in spite of the administration of iodine.

8. Muscle weakness—some workers believe that the thyroxine liberated from the thyroid has a specific action on the skeletal muscle producing asthenia. This may be illustrated by the difficulty in climbing stairs and stepping up to high places.

9. Cutaneous manifestations—flushed warm moist skin, dermographia and heat intolerance may be present in thyrotoxicosis.

B. Laboratory Findings

Of all the laboratory procedures the determination of the B.M.R. is the most important laboratory aid which can help us in establishing the diagnosis of thyrotoxicosis. The fact that this laboratory finding is merely an adjunct and not the determining factor to our diagnostic procedure must be stressed. The greatest value in determining the B.M.R. lies with the estimation of the B.M.R. level on repeated examinations and not upon the result of a single test. The elevation of the B.M.R. has some rough relationship to the severity of the thyrotoxicosis and the level has to be consistently over 15% above normal to be considered significant. In doubtful cases of thyrotoxicosis the administration of iodine or thiouracil followed by repeated B.M.R. determinations will show a general decrease of the B.M.R. in cases of thyrotoxicosis, therefore this laboratory procedure is of diagnostic value in these cases.

B.M.R. is also increased in the following: early acromegaly, leukemia, hypertension, overdosage of certain drugs, fever, pregnancy, cardiac decompensation and pernicious anemia.

C. *Diagnosis*

The diagnosis of thyrotoxicosis generally is not hard to make when the symptomatology of tremor, irritability, emotional instability, tachycardia, loss of weight and energy, goitre and ocular symptoms are present along with an elevated B.M.R. One must remember that anxiety state in the absence of thyroid pathology may give similar symptoms and even a slightly elevated B.M.R. but these cases usually subside after a few weeks of rest in bed in quiet surroundings with sedation. Cases of chronic thyroiditis have been reported presenting a typical picture of exophthalmic goitre but these conditions are rare and may be disregarded.

II Treatment

A. General Treatment

These general measures of treatment are not spectacular as compared to the specific treatment but nevertheless form an essential link in dragging the thyrotoxic patient from the throes of disaster. Reduced physical activity by bed rest, warm sponge baths and a small amount of sedation is desired. The diet should be increased in favour of proteins and carbohydrates since the B.M.R. is high and the caloric intake has to be practically doubled. Some workers have found the administration of thiamin chloride advantageous.

B. Specific Treatments

Since the causative factor in thyrotoxicosis is centred about the thyroid gland the logical step in the treatment is to eliminate the causative factor and thereby break the sequence of events leading to thyrotoxicosis. As a result the treatment of thyrotoxicosis has been approached from 3 different aspects namely; radiological, surgical and medical.

1. *Radiological treatment*

The thyroid gland is subjected to high voltage X-rays in an attempt to curb the activity of the gland, but results from such treatments have been disappointing. Up to the time of the discovery of thiouracil, the cases which are given this form of reaction followed the surgical removal of portions of the thyroid gland, in some cases severe enough to cause fatal results, thus branding thyroidectomy a dangerous operation. Plummer's discovery of the use of iodine as a pre-operative measure to ourable and therefore in the near future it will be more than likely that irradiation therapy will be discarded.

2. *Surgical Treatment*

The role of surgery in the treatment of thyrotoxicosis has been a prominent one. Since thyrotoxicosis may be the result of excessive secretion of thyroxine then removal of a portion of the gland would decrease the amount of secretion by eliminating some of the thyroxine-producing tissue. With this in mind, subtotal thyroidectomy in exophthalmic goitre or removal of the toxic adenoma have been performed, and favourable results obtained. However, some post operative thermal

reaction followed the surgical removal of portions of the thyroid gland in some cases severe enough to cause fatal results thus branding thyroidectomy a dangerous operation. Plummer's discovery of the use of iodine as a pre-operative measure to minimize the complications, rapidly reduced the operative risk of thyroidectomy. The use of drugs as a pre-operative measure will be dealt with subsequently under medical treatment.

Broadly speaking the operative principles that should be kept in mind are these:

(1) A sufficient amount of gland should be removed to eliminate the toxic symptoms, but an adequate amount of thyroid tissue should be left behind to preserve normal metabolism.

(2) Hemostasis and asepsis must be observed.

(3) Avoidance of damage to surrounding anatomical structures such as the recurrent laryngeal nerve and the parathyroid glands should be remembered.

(4) Attainment of a satisfactory cosmetic result should be strived for.

In the consideration of the first principle mentioned one can see the difficulties confronting the surgeon, for the toxic manifestations are not directly proportional to the enlargement of the thyroid, and therefore only skilled surgical judgment could determine the amount of thyroid tissue that should be removed with any degree of accuracy.

With the knowledge of the value of pre-operative treatment with iodine and lately with thiouracil, the operative mortality in subtotal thyroidectomy has been brought down to 1% or less. Following the operation the B.M.R. drops to a normal level within 2-4 weeks with disappearing toxic symptoms. Within the last 1½ years there has been much discussion as to the complete medical treatment of thyrotoxicosis by thiouracil, but as yet the follow-up on these cases has been of such short duration that surgery remains as the best method of treatment from the long-term curative point of view. Surgery is especially advised for those patients with very large goitres, for out-of-town patients who are not available for frequent check-ups and for those who cannot be trusted with self medications.

3. *Medical Treatment*

In the medical treatment of thyrotoxicosis two drugs are now offered to us. Iodine, usually in the form of Lugol's iodine has been found to be a valuable medical measure pre-operatively, and within the last 1½ years, thiouracil has been rising to the fore.

Iodine

The use of iodine as a pre-operative measure was first brought forward and popularized by Plummer. Lugol's iodine given in doses 5-15 minims t.i.d. was found to decrease the toxic symptoms, lower the B.M.R. and render the patient more suitable for operation. After iodine therapy of 7-10 days the patient is in good condition to be operated upon. The post operative course in such patients was much less stormy than those without pre-operative treatment.

The theory of the action of iodine in a thyrotoxic patient is that the thyroxine is withheld from the circulation by the action of the iodine being stored in the form of a colloid in the thyroid as evidenced by microscopic sections. When a patient is given too much iodine therapy the thyrotoxic symptoms return and the patient no longer reacts to the iodine as initially. Thus, iodine should be used only with the idea that once the toxic symptoms subside and unless there are contra-indication, a subtotal thyroidectomy is to follow.

Thiouracil

The entry of this new drug into the field of thyrotoxicosis has been a comparatively recent but dramatic one. Spectacular results have been reported by some, while in others a wave of pessimism followed its use because of fatality due to toxic reactions. The events leading up to the development of the use of this drug began in 1941, when MacKenzie and McCallum noted that effects of sulphaguanidine produced a hypothyroid state and enlargement of the thyroid gland in the rat. About the same time, Kennedy, Purves and Griesbach in New Zealand discovered that by feeding the rat a ripe seed of the Brassiae species a hyperplastic thyriod was produced. Astwood in his experimental series came to the conclusion that thiouracil is the least toxic of the 100 chemicals he tried, and since his time there have been many reports on its use.

The theory of the action of thiouracil is that it prevents the union of tyrosine and iodine into diiodotyrosine which is a precursor of thyroxine. Once thyroxine is released into the circulation thirouracil and its derivatives cannot prevent its action, thus explaining the lag period in the clinical response following its therapy. Himsworth reported that the response to thiouracil is no different in primary or secondary thyrotoxicosis. The presence of coexisting endocrine disease as diabetes mellitus, is no contraindication to thiouracil therapy. There have been reports of the treatment of thyrotoxicosis in pregnant women, in whom thiouracil produced no ill effects on the mother but an enlarged thyroid is found in the foetus. Toxic reactions which have been reported are described as headaches, vomiting, hyperpyrexia, morbilliform rashes, pruritis, oedema of legs, leucopenia and agranulo cytosis.

Thiouracil used as a pre-operative treatment has been reported to be more favourable than iodine. In the comparison of iodine and thiouracil preparation for thyroidectomy, Moore, Cope and Means in a series of 35 cases found that the B.M.R. of thiouracil patients fell to the normal level through an average range of 50 points as compared to the average +20 B.M.R. level prepared by iodine. Signs of improvement become apparent from 10-14 days following therapy and the B.M.R. reduction roughly parallels the clinical improvement. Exophthalmos and thyroid enlargement are not appreciably affected. Clute and Williams, who probably have the largest series of cases on thiouracil, treat their patients pre-operatively for a period of five to six weeks with the initial dosage of .6 gms daily for about two weeks, then .4 gms daily thereafter. These are ambulatory patients

continuing with their daily work and returning to the clinic every two weeks for check up of the blood and B.M.R. Patients are instructed to take a diet high in protein and carbohydrate and are given 5 mgm of thiamin chloride daily. They are operated upon within two days of admission and returned home six to seven days post operatively.

The operative course in thyrotoxic patients treated in this way is remarkable only in its smooth course, and they react as normal individuals to a modern surgical procedure with no marked change in pulse or blood pressure. However the gland is more vascular and the bleeding may be a little more profuse. Their post operative course is equally smooth and uneventful. Thus, in thiouracil, surgery has found a valuable addition to its armamentarium in the pre-operative treatment of the patient, a highly important phase of surgery.

With the remarkable results obtained in the pre-operative treatment it is but a small step to take to endeavor to treat thyrotoxicosis as a purely medical problem. Clute and Williams reported a series of 115 patients of which 81 are treated with thiouracil, and 34 treated with thiouracil+thyroidectomy. The latter series of 34 cases required thyroidectomy, not because it was thought that the toxic condition cannot be controlled by thiouracil, but because of such conditions as excessively large goitres and adenomas, difficulties due to the time factor and toxic reactions to the drug. The series of 81 cases on thiouracil alone is still under observation, the duration being over 1 year now. Clute and Williams are of the opinion that it may be possible to eliminate surgery in the treatment of many cases of thyrotoxicosis.

The dosage set forth by most authorities is .6 gms daily initially. This is reduced to .2-.1 gms according to the B.M.R. level, blood picture and signs and symptoms. A rise in the B.M.R. after 2 months' therapy is usually an indication of inadequate dosage. Under medical treatment some patients claimed marked improvement of subjective symptoms within 24-48 hours. This was perhaps due to the psychological effect, or to the sedative effect, since the chemical structure of thiouracil closely resembles that of the barbiturates. The decrease in the B.M.R. is more rapid in severe cases but it takes 5-6 weeks before the normal B.M.R. level is regained. Less severe cases require only 3-4 weeks to attain the normal but the fall in B.M.R. is less spectacular. In patients who have had previous iodine therapy, a lag in the clinical response of about 3 weeks' duration is evident, but upon further treatment the B.M.R. decreases. In most cases the thyroid gland under treatment decreases in size and increases in firmness, but it is possible to exceed the optimal dose and cause an increase in the size of the thyroid.

Before endorsing the strict medical treatment scheme certain questions come to our mind.

1. Is the action of thiouracil such that after a period of time of treatment the thyroid gland will return to normal function, and if so, how long should the course of treatment last?

2. Or is the thyrotoxic patient forced to take thiouracil for the rest of his life, always being exposed to the danger of toxic reactions?

3. With the thiouracil stimulating the thyroid gland to a high degree of hyperplasia, is there danger of inducing toxic goitres to malignancy?

These are but a few of the questions which we hope will be answered by a follow-up series of cases of longer duration.

Prognosis

On the whole the prognosis for cases of thyrotoxicosis is good, for the clinical features can be markedly improved if not totally abolished by the present method of treatment. With our knowledge of the pre-operative treatment advancing almost daily and our surgical techniques improving, the operative mortality is being steadily whittled down to 1% or less. This means that the average case of thyrotoxicosis can be treated satisfactorily with only a small risk. In the future we may be able to treat these patients strictly from the medical point of view and yet attain the criteria for a satisfactory cure.

Summary

The clinical signs and symptoms and other aids which may help to establish a diagnosis of thyrotoxicosis have been summarized. An attempt to describe the general method of treatment from the radiological, surgical and medical aspects has been carried out, and the relative merits of each evaluated, with special emphasis on the new drug, thiouracil, as to its history, action and use. Lastly, the prognosis in cases of thyrotoxicosis is indicated as being generally favourable.

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ENDOMETRIOSIS

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DEFINITION:

Endometriosis is the presence of endometrial like tissue in abnormal situations. These growths may be found almost anywhere in the pelvis or in the abdominal cavity below the umbilicus, on the peritoneal surface of pelvic organs or retroperitoneally. Common situations are on the ovaries and in the recto-vaginal septum.

INCIDENCE:

Endometriosis is a disease which occurs mainly between the ages of 23 and the menopause. Since this disease has so many manifestations many of which are unrecognized by surgeons and pathologists at operations and autopsies and since there are numerous borderline cases with little clinical significance, the incidence of this disease is essentially unknown. But the diagnosis of endometriosis is on the increase. In his major operations G. R. Goodall of Montreal found evidence of some form and stage of endometriosis in 25% of all cases. Meigs recorded in 1941, that of 400 private abdominal cases, 36% were considered to have endometriosis grossly and 28% showed it microscopically. This contrasts with 8.3% by gross diagnosis and 5.8% by microscopic diagnosis of 400 Massachusetts General Hospital ward abdominal cases. Thus we see that endometriosis is definitely a social-economic disease occurring much more frequently in the higher social and economic strata of womanhood. All authors agree that the greatest incidence of endometriosis is found in the last half of the fourth decade of life, a period of reduced fertility which is still in the child bearing age.

FAMILIAL TENDENCIES:

Several observers have found similar types of endometriosis in two or three sisters of the same family, where in some cases the mother was operated on for endometriosis. In one such case three daughters had this condition and two of them had spontaneous intraperitoneal rupture of large chocolate cysts necessitating operation for an acute abdomen.

ETIOLOGY:

This condition may truly be called a disease of theories. It is thought that the immediate cause of endometriosis is hyperestrinism since the ovaries seem to be necessary for the initiation and continuation of the disease. Estrin is the growth hormone causing the hypertrophies of all the organs of generation preparatory to pregnancy. Most of the manifestations accompanying endometriosis are of the nature of hypertrophies and activation of tissues. This immediate cause may be superimposed on a personal susceptibility,—some constitutional dyscrasia in those individuals developing this disease. There also seems to be within this personal susceptibility, an organ susceptibility, as in some cases the uterine manifestations are dominant, in others the peritoneal manifestations predominate. Other predisposing causes are the age and social-economic status of the woman.

CLASSIFICATION:

1. *Uterine Endometriosis or Endometriosis Interna*
   - (a) Endometrial Intra-uterine Endometriosis
     1. *Mixed* (ordinary endometrial hyperplasia or "Swiss Cheese" hyperplasia as seen in Functional Uterine Bleeding).
     2. *Stromatous* (in which the endometrial hypertrophy is mainly due to increase in stroma).
   - (b) Parietal Uterine Endometriosis
     1. *Mixed* (this is a kind of diffuse invasion of the uterine wall by an infiltration into the spaces between the muscle bundles, the stroma cells usually preceding the glandular elements).
     2. *Stromatous* (in which the uterine wall is invaded diffusely to abnormal depths by the stroma cells of the uterine endometrium).
   - (c) Adenomyoma
     1. *Mixed* (in which the invasion by both endometrial elements is accumulated in localities in the uterine walls to form definite tumour growths causing asymmetry).
     2. *Stromatous* (in which the tumours are made up wholly of stroma cells and devoid of glandular elements).

2. *Extra-uterine Endometriosis or Endometriosis Externa*
   - (a) Ovarian Endometriosis
   - (b) Intraperitoneal and Retroperitoneal
     1. Intestinal implants
     2. Rectum and mesorectum
     3. Tubal and Broad ligament endometriosis
     4. Parovarian
     5. Round ligament
   - (c) Endometriosis of the Umbilicus and Ant. Abdominal wall
   - (d) Endometriosis of the Pelvic lymph glands
   - (e) Vesical Endometriosis
   - (f) Vaginal Endometriosis
   - (g) Vulvar Endometriosis.

This classification has its basis in the organs that are affected by the disease and not in the origin of the disease as all cases of endometriosis take their origin from some part of the endometrium. The chief reason for the division of this classification into uterine and extra-uterine types is that since the uterus is so poorly supplied with sensory nerves, uterine endometriosis is a symptom free disease usually discovered by accident or by its signs, while extra-uterine endometriosis is recognized by its symptomatology, disturbance of function, destructiveness and palpable signs. Moreover, extra-uterine endometriosis is overwhelmingly respon-

sive to the cyclic menstrual changes and there is no outlet for its vascular extravasations unless the pressure finds an outlet by bursting into areas of less pressure resistance e.g. when a blood collection with its desquamated cells bursts into a portion of the peritoneal cavity and thus helps to spread the disease. Intra-uterine endometriosis on the other hand has the normal outlet for its menstrual secretions and the adenomyosis type deep in the wall of the uterus does not respond to menstrual changes.

ORIGIN:

At the beginning of the century Ivanoff proposed the theory that extra-uterine endometriosis might arise from a metaplasia of the pelvic peritoneum. Robert Meyer also championed this theory. Scott of Toronto General Hospital is dubious of this theory as he finds it hard to picture the serosal cells changing to both epithelial and stromal cells at just the same time and in just such a manner as to produce endometrial-like tissue. In 1896 Von Recklinghausen suggested that endometrial tissue found in the uterine wall might be due to activated embryonic cell rests. In 1921 Sampson expounded his "Spill" and "Implantation" theory i.e. the escape of endometrial tissue through the fimbriated ends of the tubes, spilling into the peritoneal cavity, implanting themselves in various sites and capable of reproducing in suitable soil the menstrual cyclic changes synchronously with the uterine menstrual phases. These implants have the power to invade the organ-hosts and being closed cavities, menstruate into the cavities each month causing dilatations into cystic collections varying in size from those of microscopic dimensions to growths as large as a grapefruit. These are named chocolate cysts. In 1925 Sampson demonstrated that the endometrial cells could also spread by permeating lymph channels and that the mucosa of the tubes could also be shed into the peritoneal cavity and implanted. This would be called "Salpingiosis". Jacobson's experiments supported Sampson's theory. Uterine curettings from rabbits in heat were sowed in the abdominal cavity and implants were formed in 83% of these rabbits.

Sampson has contended that the virulence of endometriotic implants is heightened by successive implantations and that the ovary is the best "hot house" soil. This may have something to do with the ovary being the producer of the causative agent. King believes that the chocolate-coloured cysts of the ovary are follicular in origin. It has long been known that the cysts derived from the Graafian follicles and especially from atretic follicles, may be lined by epithelium which cannot be distinguished from that of the endometrium.

PATHOLOGY:

Endometriosis in general may be divided into acute and chronic.

Acute

Gross: In the uterine type the hypertrophy and softening of the uterus may be so marked as to be confused with a pregnancy of two to three months. In the intraperitoneal type of the acute major form of the disease (instead of a few black "beads" and the characteristic pucker-

ing about these on the ovarian surface, in the Pouch of Douglas or on any susceptible peritoneal surface) we find that all the pelvic organs are a conglomerate mass, stained with old and new blood, blood stained peritoneum, blood cysts and tissue sclerosis. The disease may be spontaneously arrested at any stage of its development.

Microscopic: The endometriotic cells have the normal characters they usually possess at the height of the sexual age. They are clear oval cells with clear oval nuclei, turbid cytoplasm, clearly defined nuclear chromatin and skein-like arrangement.

Chronic

Gross: In the uterine type the uterus becomes symmetrically hard and tender. In the intraperitoneal form there is produced sclerotic changes in the peritoneum of the nature of a deposit of colloid substances in the subperitoneal tissues and a similar sclerosis first of the Tunica Albuginea and later of the deeper tissues of the ovarian stroma. Dense fibrous adhesions are formed causing fusion of the affected contiguous organs, ending in a conglomerate mass of all the pelvic organs, firmly adherent to the fasciae of the pelvic wall.

Microscopic: In the more common chronic forms the cells tend to lose their oval to round shapes and become more spindle shaped and elongated approaching in the extreme case the character of connective tissue. The nucleus also becomes elongated proportionately with the cell cytoplasm. (All types of cells from the oval to the extremely elongated may be encountered in the same section, so that these signs of chronicity are really due in part to the compression of the tissues of the organ invaded.)

The agent which causes endometriosis operates in most cases not only upon the endometrium causing it to proliferate and infiltrate, but also exercises a stimulating proliferative influence to a much lesser degree of course upon other tissues of the generative organs, such as those of the uterus, ovaries, cervix and vagina. This same causative agent exercises profound changes upon the lower abdominal peritoneum characterized by a diffuse sclerosis, usually more pronounced in the utero-vesical pouch and pouch of Douglas, and frequently involving the anterior parietal peritoneum as high as the umbilicus.

Chocolate or "Tarry" Cysts. These are almost characteristic of endometriosis. These blood extravasations from the endometrial implants are usually of the same degree of "chocolatiness" by virtue of absorption which affects simultaneously all endometrial blood extravasations.

Old Blood Extravasations and Hemic Stains. These are due to the bursting of the above cysts into the peritoneal cavity. This old blood on the free peritoneal surface often becomes organized and is soon covered by peritoneal cells as an encapsulated body. These appear as characteristic pigmented areas on the surface of the peritoneum.

The spontaneous rupture of the blood cysts into the general peritoneal cavity may give rise to "peritoneal secondary contamination".

Invasive Properties of Endometriosis:

Endometriosis is an invasive disease, the endometrial cells invading and pushing along the lymph channels. But these endometrial tissues are not destructive in the same sense as a malignant new growth, merely pushing the normal tissues aside as they multiply in the lymph channels. In most instances not even the delicate lining of the lymph spaces is destroyed, but may suffer from compression. Blood vessels themselves are not invaded. There is no necrosis of tissue in the immediate vicinity of these invading cells and there is no cachexia. Difficulties arise only when the functions of essential organs are obstructed by compression. Many endometrial cells in the form of emboli in the lymphatic stream may reach different parts of the body but since the terrain outside the pelvis is unsuitable for their growth they do not last very long.

Symptoms and Signs:

The site and the type of the disease determine the symptomatology.

1. *Vulvar Endometriosis.* This is a progressive growth the nature of which must be determined by biopsy. (These are usually of the stromatous type and therefore do not show menstrual changes and the typical chocolate cysts.) Its nodules when multiple tend to grow in parallel lines.

2. *Vaginal Endometriosis.* There are two types,—implanted and perforating. In the vagina the implanted type, when a large patch is involved, is generally recognized in a vaginal examination as an unusually smooth velvety surface in marked contrast to the rest of the vaginal wall. Rarely does the disease involve more than two square inches of the vaginal vault. Usually the area is not larger than a pea and they are often multiple. When menstruating they are very red and ooze blood. In the perforating type, the nodule, usually in the posterior vault, is an extension from the recto-vaginal tissues. These nodules become purple and red in the menstrual period.

3. *Endometrial Intra-Uterine Endometriosis* is usually a symptomatic but may be a cause of menorrhagia.

4. *Uterine Parietal Endometriosis.* This is seldom diagnosed before operation and can be confirmed only by biopsy. In the major types there is enlargement of the uterus.

5. *Ovarian Endometriosis.* The chief symptom here is premenstrual or menstrual pain. In the bimanual examination of advanced cases the pelvis is felt to be filled with masses, and nodules are usually felt in the pouch of Douglas.

Symptoms referable to other organs of the pelvis depend upon extension of the disease to these organs or their attachments. Symptoms suggesting appendicitis or bowel obstruction are not uncommon. Rupture of a large cyst into the peritoneal cavity may present a picture of general peritonitis. In old peritoneal endometriosis, pain of a constant boring character may persist due to dense adhesions under tension. This pain may be increased in the premenstrual phase. Singularly,

endometriosis, even of the most extensive character, rarely produces cachexia or any appreciable depreciation of normal health.

Differential Diagnosis:

Intraperitoneal endometriosis must be differentiated from chronic pelvic inflammation. (Less leucocytosis, normal sedimentation rate, etc.) In cases of bowel obstruction, carcinoma, inflammation and diverticulitis we may mistakenly diagnose endometriosis. The now recognized frequency of the disease makes endometriosis a factor in the differential diagnosis of many gynecological conditions.

Prognosis:

This depends of course upon the type and severity of the lesions. Endometriosis in itself is rarely fatal except perhaps in such complications as intestinal obstruction, superadded infection, etc.

Endometriosis and Pregnancy:

"Endometriosis and pregnancy" is somewhat of a paradox as this disease has usually been associated with sterility. Haydon reported a relative sterility rate of 53%. Possibly this is due to associated pathology such as fibroids. Dyspareunia in endometriosis may reduce coitus and this may be a factor in the apparent lack of fertility in these patients. But despite the sterility statistics so frequently given for patients with endometriosis, a collected series of endometriosis cases of all types complicating pregnancy is evidence enough that such patients can and do become pregnant. A review of the reported cases of endometriosis in pregnancy reveals a high incidence of elderly primiparas. Adenomyosis may possibly be a reason for spontaneous rupture of the uterus early in pregnancy. Extra-uterine endometriosis complicating pregnancy is most commonly found, according to the literature, in the pouch of Douglas. Usually, this is symptomatic because of vaginal extension giving rise to a brownish or frank bloody discharge during pregnancy. This must be differentiated from threatened abortion. Ovarian endometriosis is the second most commonly reported type found during pregnancy.

Treatment of Endometriosis:

Prophylaxis. Meigs is of the opinion that endometriosis is a disease arising out of neglected function of reproduction and so he advises early marriage and pregnancy as a means of prevention.

Treatment. Since the ovaries are essential to the initiation and continuation of the disease, removal of the ovaries or arrest of their function by X-ray usually causes an abrupt ending to the disease. A few types may be treated by less drastic measures. If the condition is confined to the uterus only, this organ may be removed, the ovaries being left intact. Vulvar endometriosis may be treated by local excision or radiation.

Vaginal endometriosis may be treated by destruction with the electric cautery or by the local use of radium. Our treatment of endometriosis is greatly influenced by the age of the patient and the extent and character of the disease. We would, of course, not be quite so hesitant about inducing artificial menopause in a patient

who is already nearing the climacteric. Rest, nutritious food, and climatic treatment are all valuable adjuvants in the treatment of any type of endometriosis. Indeed, many cases are cured spontaneously without any other treatment, or the disease may become quiescent and retrograde changes occur.

In very advanced acute endometriosis, radical removal of the ovaries is the only logical solution.

To summarize, every case of endometriosis must be treated on its own merits, taking into consideration the age of the patient and extent and character of the disease.

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CARBON MONOXIDE ANOXEMIA

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Very early medical literature contains references to carbon monoxide poisoning. This gas was used by the Greeks and Romans for the execution of criminals and as a means of committing suicide. Poisoning by carbon monoxide is a serious and common condition, and one frequently encountered by the average physician. During times of peace it accounts for more deaths than all the other gases combined.

Carbon monoxide derives its physiological interest from its property of combining with hemoglobin in a manner apparently identical with oxygen. The hemoglobin, however, has a very much greater affinity for carbon monoxide than for oxygen, and therefore carbon monoxide is a potent cause of anoxemia when it is mixed with the inspired air.

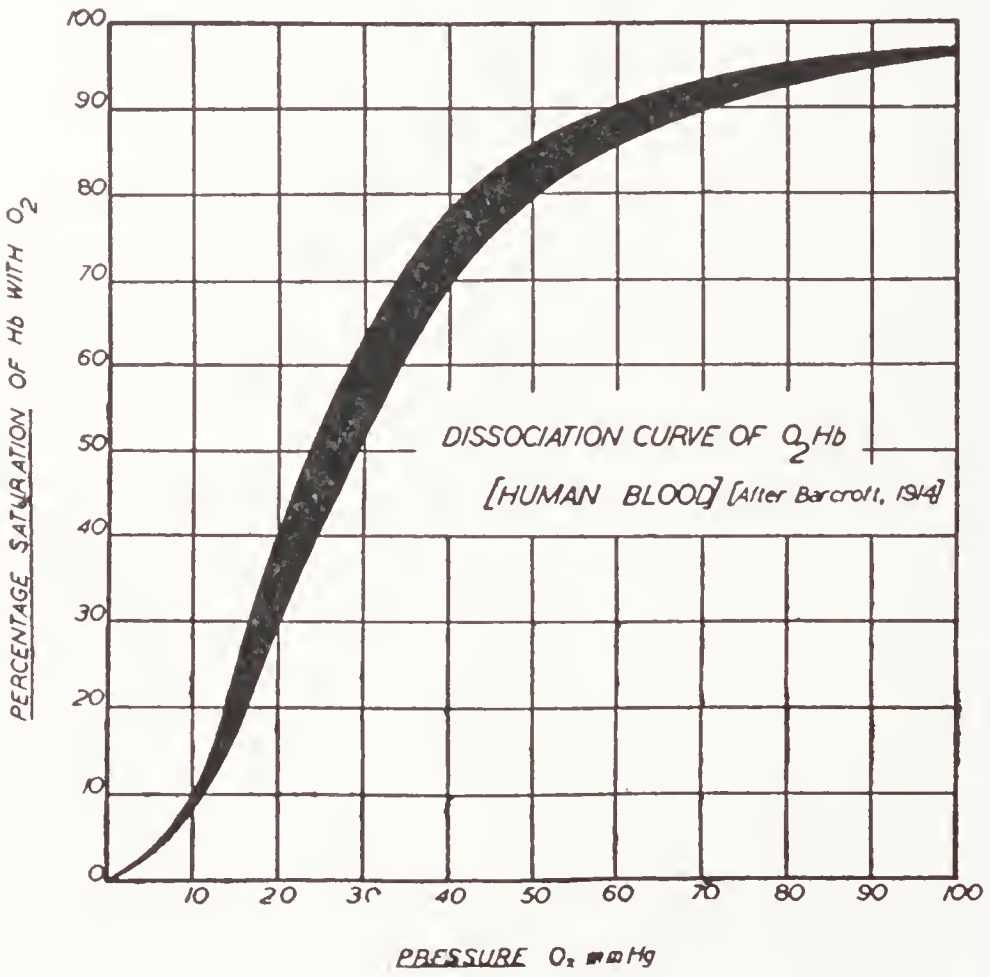

FIGURE 1

EFFECT OF CARBON MONOXIDE ON THE OXYGEN DISSOCIATION CURVE

Oxygen enters into chemical combination with the iron of the hemoglobin molecule, to form *oxyhemoglobin*. On the other hand, oxygen is readily released from its combination with hemoglobin when its tension in the surrounding medium is reduced. Hemoglobin from which the oxygen has dissociated is called *reduced hemoglobin*. The relationship between the partial pressure of oxygen and the percentage saturation of the hemoglobin with oxygen can be expressed in the form of a curve, the *oxygen dissociation curve of hemoglobin* (Figure 1).

Carbon monoxide combines with hemoglobin in the same proportion as does oxygen, to form *carboxyhemoglobin*. In the absence of oxygen, the curve relating the partial pressure of carbon monoxide to the percentage saturation of the hemoglobin with carbon monoxide is identical in shape to that of oxygen. The position of either curve is influenced by the same factors; as, pH, temperature, and salt content of the blood.

The difference lies in the range of partial pressure. While the hemoglobin of human blood becomes half saturated with oxygen at a partial pressure of about 30 m.m., it is half-saturated with carbon monoxide, under the same conditions of pH, temperature, and salt content, when exposed to a partial pressure of carbon monoxide of about 0.125 m.m.

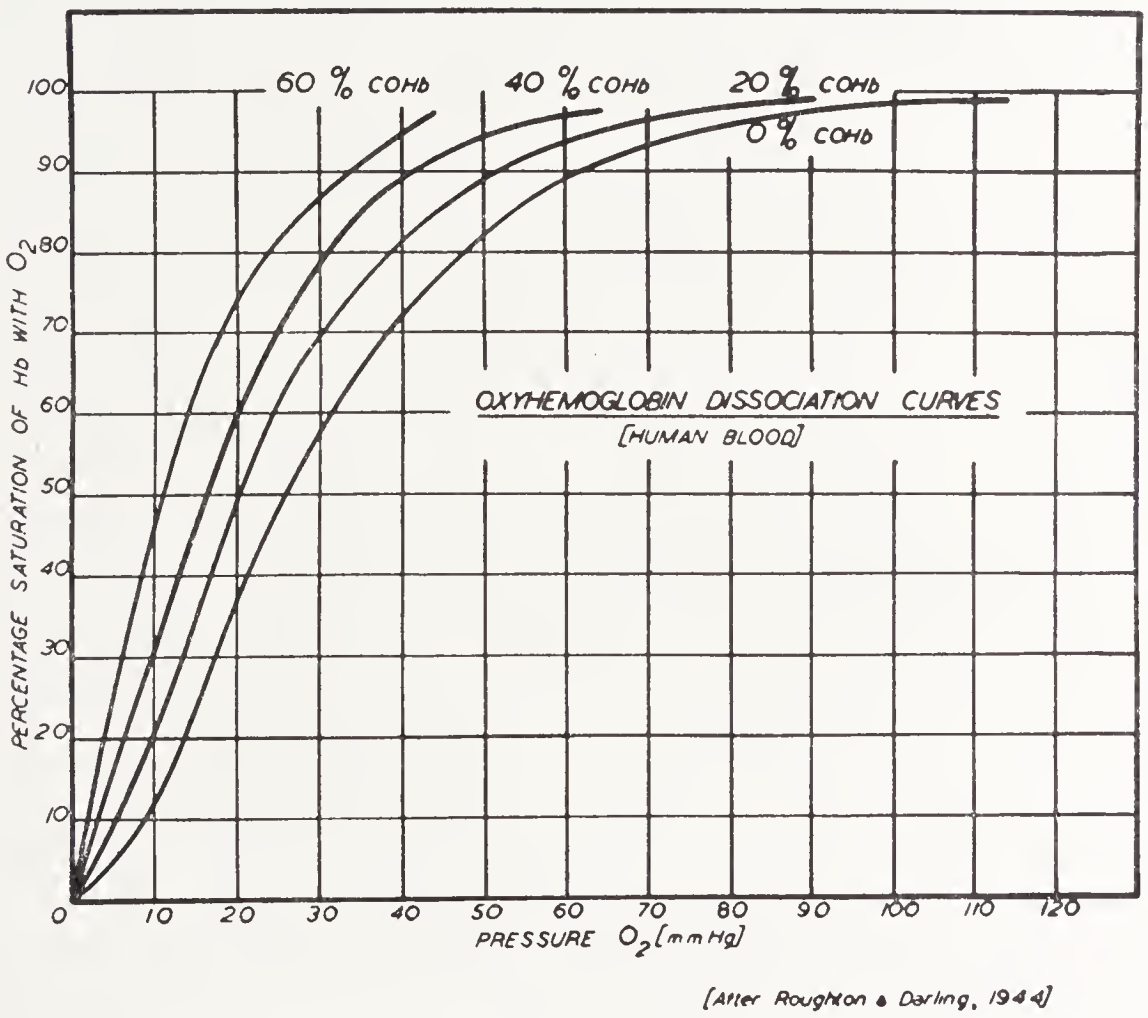

FIGURE 2

When blood is exposed to a mixture of oxygen and carbon monoxide, the hemoglobin is divided between the two gases obeying the law of mass action. The proportion of hemoglobin combined with either gas depends upon the relative partial pressure of oxygen and carbon monoxide, and upon a constant which expresses the relative affinity of the blood for the two gases (Haldane and Smith, 1897).

$$\frac{[HbCO]}{[Hbo_2]} = \frac{K[CO]}{[O_2]}$$

On the basis of this fact partition curves relating the partial pressure of carbon monoxide to the percent saturation of the hemoglobin with carbon monoxide, may be constructed for any blood.

The partial saturation of the blood hemoglobin with carbon monoxide shifts the oxygen dissociation curve of the remaining hemoglobin progressively to the left, and also makes the curve less S-shaped and more hyperbolic as shown in Figure 2 (Roughton and Darling, 1944). This shift is known as the "Haldane Effect".

Significance of the Shift of the Oxygen Dissociation Curve

This shift of the oxygen dissociation curve indicates that blood partially saturated with carbon monoxide, must cling to its oxygen with greater tenacity. Thus the tissues have much more difficulty in obtaining oxygen from the blood than they do when the oxyhemoglobin from the blood is reduced to a corresponding extent by anaemia.

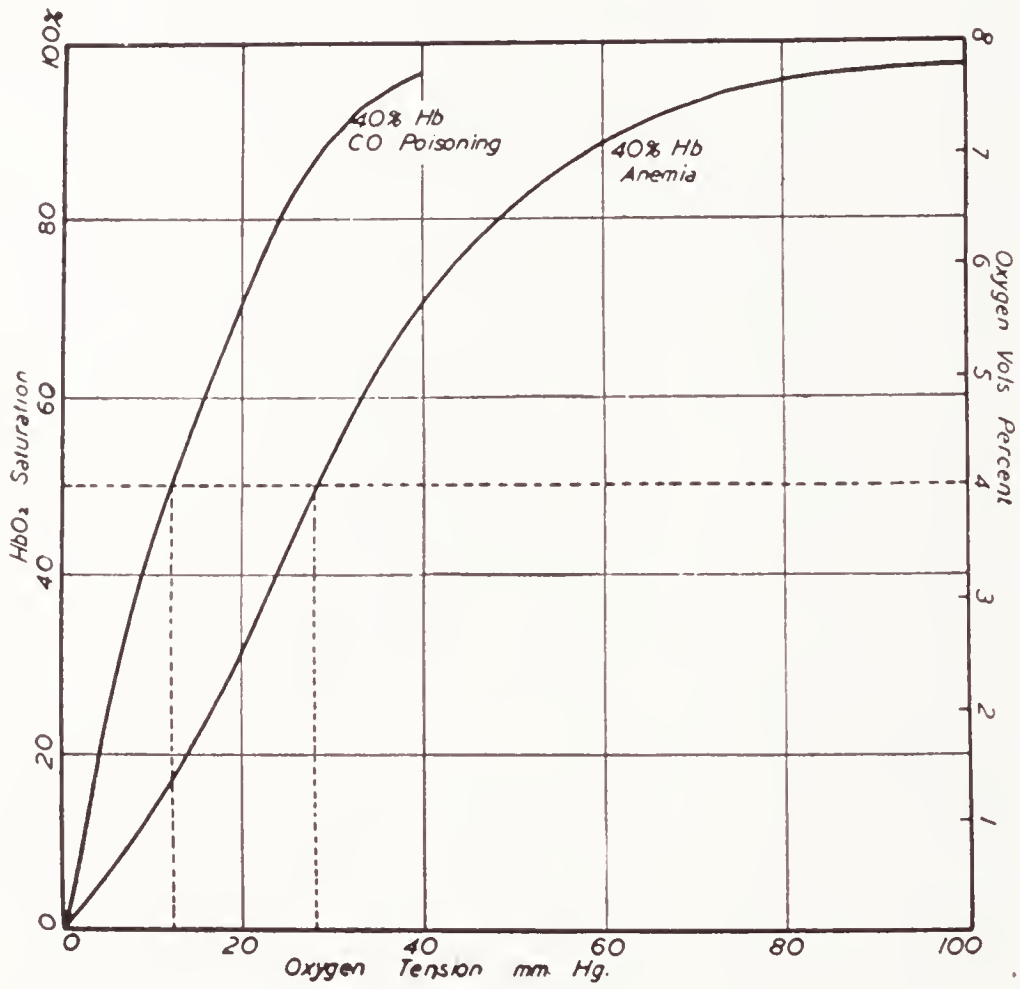

Figure 3

The above deduction explains why an individual whose blood is 60 percent saturated with carbon monoxide is almost helpless, but an individual whose blood contains only 40 percent of the normal amount of hemoglobin behaves normally, and can often carry on his work. The partial pressure of the oxygen in the arterial blood, and dissociation of oxygen from the oxyhemoglobin is quite different (Figure 3). When the blood is partially saturated with carbon monoxide, the alteration in shape and position of the dissociation curve of the remaining oxyhemoglobin produces a marked lowering of the partial pressure at which oxygen is available for tissue metabolism (Stadie and Martin, 1926). Consequently, profound anoxemia occurs in carbon monoxide poisoning, although the blood may contain two or three times the amount of oxygen necessary for normal tissue function.

Value of Equilibrium Constant (K)

The value of the equilibrium constant (K) is practically independent of pH, salt content, dilution of the blood, or purification of hemoglobin (Roughton, 1934). Factors such as carbon dioxide tension, therefore, which markedly affect the oxygen or carbon monoxide dissociation curves of the blood, have no effect on the partition of hemoglobin between oxygen and carbon monoxide.

The partition, however, is greatly affected by light, and also temperature. Ultra-violet light hastens the dissociation of carboxyhemoglobin in the presence of oxygen. The great affinity of carbon monoxide for hemoglobin is due to the fact that carboxyhemoglobin dissociates very much more slowly than oxyhemoglobin, although oxygen combines with hemoglobin about 10 times as fast as does carbon monoxide under similar conditions of pH, temperature and concentration of reagents. The value of K varies inversely with the temperature at which equilibrium occurs.

Rate of Absorption and Elimination of Carbon Monoxide

The relationship between the partial pressures of oxygen and carbon monoxide and the saturation of the blood with carbon monoxide enables one to predict approximately the final blood saturation of a man who is breathing air containing a small amount of carbon monoxide, but it gives no information as to the speed with which the saturation will be reached. The rate at which the percentage saturation increases in different animals is proportional to the respiratory exchange per unit of body weight. In small animals absorption is more rapid and final equilibrium reached more rapidly than in man. The mouse reaches equilibrium with the mixture it is breathing twenty times as rapidly as man. Thus mice and birds have been used for detecting concentrations of carbon monoxide harmful to man.

In the human being the rate at which the body takes up carbon monoxide depends mainly on the partial pressure of carbon monoxide in the air breathed, the volume of pulmonary ventilation, and the blood flow through the lungs. Thus when an individual is doing muscular work, the process of absorption is more rapid.

The rate of elimination of carbon monoxide is governed by the same factors as its absorption. The elimination of carbon monoxide is hastened by any factor that increases the volumes of pulmonary ventilation, the circulation rate of the blood, or that raises the partial pressure of oxygen in the alveoli.

Mode of Action of Carbon Monoxide

The percentage saturation of the blood with carbon monoxide represents fairly accurately the degree of anoxemia to which the individual is subjected, because carbon monoxide acts by preventing the normal carriage of oxygen in the blood, and not as a direct tissue poison. It is known that carbon monoxide can act as a tissue poison by inhibiting the enzymic oxidative systems in the tissues, but this effect is only evident at relatively high partial pressures of the gas (Killick, 1940). Carbon monoxide acts as a physiologically inert gas, except for its power of combining with hemoglobin. This fact is confirmed by the indifference to carbon monoxide of animals and tissues without hemoglobin; as, cockroaches.

Certain toxic effects of carbon monoxide may be due to the high affinity for this gas of some compounds related to hemoglobin. These compounds are of importance in tissue metabolism and their combination with carbon monoxide may account for the pathological changes which follow carbon monoxide poisoning, but which do not occur in the anoxemia of severe hemorrhage.

Symptoms of Carbon Monoxide Anoxemia in Man

The symptoms of acute carbon monoxide poisoning in man, are closely associated with the degree of saturation of the blood with carbon monoxide. The succession of symptoms is shown in Table 1. The symptoms are accentuated by muscular exercise, and more serious symptoms appear at a lower percentage saturation of the blood when the individual is working than when he is quiet. The rate at which the percentage saturation of the blood increases may also modify the symptoms. During exposure to low concentrations of carbon monoxide, the symptoms appear gradually, and their severity varies with the duration of the exposure.

Table I

PER CENT SATURATION OF BLOOD WITH CO.	SYMPTOMS
0-10	Nil.
10-20	Nil at rest; during exercise tightness across forehead, slight headache.
20-30	Frontal headache may occur at rest; exertion causes dizziness, palpitation, and hyperpnea.
30-40	At rest, headache, frontal or occipital, increased pulse rate, deeper breathing, palpitations, nausea; exertion causes dizziness, dimness of vision, abnormal increase of pulse rate and respiration, sometimes collapse.
40-50	All symptoms more marked; vision, hearing, and intelligence begin to be impaired; muscular weakness on attempted exertion, with greater likelihood of collapse. Nausea and vomiting.
50-60	Syncope; increased respiration and pulse rate; coma.
60-70	Coma with depressed heart action and respiration; possibly death.
70-80	Weak pulse and respiration; respiratory failure and death.

From Sayers, Yant, Levy and Fulton (1929) and Killick (1936).

Sources of Carbon Monoxide

Carbon monoxide may be encountered wherever carbon or its compounds are burned with insufficient oxygen. Exhaust gases of internal combustion engines and illuminating gas are the most common sources of carbon monoxide contamination.

Effects of Carbon Monoxide Anoxemia

The effects of carbon monoxide anoxemia on various parts of the body have been admirably summarized by Drinker (1938) in his monograph on carbon monoxide poisoning.

Central Nervous System

The tissue of the central nervous system is most easily damaged by anoxemia. After death from carbon monoxide poisoning, the brain is found to be hyperemic

and edematous, and usually shows numerous punctate hemorrhages (Hiller, 1924). These appearances of the brain are considered outcomes of the toxic action of carbon monoxide on capillaries. Microscopical evidence of nerve cell and nerve fiber degeneration was observed in many cases of carbon monoxide poisoning (Hsu and Cheng, 1938).

These pathological changes observed in human beings killed by carbon monoxide have been paralleled by extensive experimental pathological investigation on dogs. These results were compared with the effects of simple oxygen lack, and the pathological findings were very similar. This similarity does not support the view that carbon monoxide has a toxic effect on the capillaries, and suggests that the damage to blood vessels results from oxygen lack.

The headache resulting from carbon monoxide anoxemia may be due to an increased pressure in the cerebro-spinal fluid, since measures designed to reduce this pressure also alleviates the headache.

Intellect

The symptoms of carbon monoxide anoxemia resemble those of drunkenness, and a man suffering from this ailment cannot be held responsible for his actions. He is always quite confident that he is perfectly sane and reasonable, though he may be unable to walk or write properly, cannot remember what has just happened, and cannot properly interpret his visual impressions (Haldane and Priestley, 1935). The person affected with carbon monoxide anoxemia may be brought to the very verge of unconsciousness without appreciating in the least degree that anything is wrong. The subtlety of these mental effects cannot be too much emphasized, for it greatly enhances the chance of the occurrence of carbon monoxide poisoning.

In spite of these serious changes in the intellect during carbon monoxide anoxemia, permanent mental or neurological disease rarely follows.

Special Senses

Eye—Haldane (1912) noticed that his vision was "not so good" when his blood was 40 per cent saturated with carbon monoxide. The ability of the poisoned person to estimate the degree of visual defect is greatly reduced. During the development of carbon monoxide asphyxia, the subject may see flashes of light and dark specks before his eyes, these phenomena usually just preceding total blackness.

The differential light sensitivity of the retina has been shown to have a high degree of sensitivity to anoxemia, either anoxic or carbon monoxide (McFarland et al. 1944). This visual test has proved to be so sensitive, that even the effects of small quantities of carbon monoxide absorbed from cigarette smoke can be clearly demonstrated. Deep inhalation of the smoke from a single cigarette causes an increase in the carboxyhemoglobin saturation of about 2 per cent. Although previously such a small amount was considered totally insignificant, it nevertheless causes a distinct impairment of visual sensitivity. After three cigarettes, the blood carboxyhemoglobin is raised to 4 per cent and the effects in one's visual sensitivity is equal to that at an altitude of about 8,000 feet. A similar rise in carboxyhemo-

globin produced by inhalations of pure carbon monoxide produces about the same effect. On the other hand, the smoking of three cigarettes by this subject, without inhaling, resulted in no visual change. In this case there was no change in carboxyhemoglobin although the nicotine absorption is about 60% as great as during smoking with inhaling. It thus appears likely, that only the carbon monoxide is responsible for the visual effect of smoking.

Cases of permanent damage to vision have been reported. The most interesting case of visual damage from exposure to carbon monoxide was reported by Adler (1944). The subject was a survivor from the Cocoa-Nut Grove disaster in Boston. The fundamental disturbance consisted of the patient's inability to perceive whole objects visually. Only parts of the whole were perceived, and their correct relation was not recognized. This resulted in an inability to read, to copy letters and geometric figures, to recognize pictures or objects on short exposure. However the ability to write was not impaired.

Ear—Hearing is the last of the special senses to be lost as carbon monoxide anoxemia develops. Similar to the eye, a variety of auditory disturbances may appear prior to the loss of consciousness. Permanent damage to hearing is very infrequent.

With the present-day methods of accurately measuring auditory acuity, the effect of smoking on hearing would prove an interesting line of research.

Susceptibility to Infection

Acute carbon monoxide poisoning has often been reported to increase susceptibility to disease. In support of this statement, investigators have drawn attention to the fact that pneumonia frequently follows acute carbon monoxide poisoning. Other investigators are skeptical of the suggestion that carbon monoxide has any specific affect in increasing susceptibility, and associate the incidence of pneumonia with any long period of unconsciousness, irrespective of the cause.

Much conflicting evidence has been presented regarding the diminished resistance to infection as one of the effects of chronic exposure to carbon monoxide.

Heart and Blood Vessels

During the period of carbon monoxide anoxemia, the heart rate at rest is unaffected until the saturation of the blood reaches 25 to 30 per cent (Killick, 1936). The pulse rate increases approximately in proportion to the saturation of the blood with carbon monoxide, but as anoxemia becomes more severe, the heart begins to fail. During partial carbon monoxide anoxemia, exercise causes a marked increase in pulse rate. No direct toxic action of carbon monoxide on the heart has been reported. All reactions observed are regarded as indirect effect of anoxemia.

The most characteristic cardiac effect of carbon monoxide anoxemia is heart block, which does not appear except under extreme degrees of asphyxia. Early in asphyxia, there are occasional ventricular extrasystoles and T-wave inversion. The length of this paper limits discussion along this line.

Carbon monoxide does not affect the blood vessels except in very severe cases

of poisoning where hypertension and arteriosclerosis are evident (Drinker, 1938). The pathological findings indicate that in extremely serious poisoning, the fragility of the capillaries may be increased, and thrombosis and embolism may result.

Respiration and Chemical Changes in Blood

Since respiration and the acid-base equilibrium of the blood are so closely related, they are considered here under the one heading. Most investigations have observed a decrease alkali reserve but their interpretations vary greatly. During the period of anoxemia respiration increases greatly.

Blood Cells

Some investigators state that erythrocytes may show slight degree of degeneration a short time after poisoning, but this damage is not severe enough to prevent the gradual increase of circulating red cells and pure carbon monoxide, inhaled in small amounts, results in a definite polycythemia.

More recent investigations (Brieger, 1944) do not confirm the initial observation of an acute increase in the circulating red cells in the early stages of carbon monoxide poisoning. A series of experiments on both dogs and men did not demonstrate an early increase of hemoglobin and red blood cells in the circulating blood. On the contrary, even decreases of hemoglobin and red blood cells were encountered.

A significant polycythemia was a late effect of high blood saturation with carbon monoxide such as encountered during acute carbon monoxide poisoning. Polycythemia was most marked several days after the exposure and long after all the carbon monoxide had disappeared from the blood. Reticulocytosis and appearance of normoblasts in the circulating blood indicated a stimulation of haemopoietic tissue in the bone marrow.

Blood Coagulation

Carbon monoxide has been accused of both acceíerating blood coagulation and of delaying it.

Cases of fatal carbon monoxide asphyxia have been accompanied frequently by hemorrhage and thrombi, but these effects are believed due to the effect of anoxemia on the capillary walls rather than changes in the blood itself.

Effect on Reproduction and Sex

Carbon monoxide anoxemia appears to affect the gonads. Prolonged exposure to low concentrations of carbon monoxide has been shown to greatly reduce the fertility in experimental animals. Exposures to carbon monoxide also causes a tendency for females to abort.

Methods for the Determination of Carbon Monoxide in Blood

The determination of carbon monoxide concentration in blood is a direct means of evaluating the hazards of exposure of individuals to carbon monoxide. The most common methods currently used are described briefly.

Microgasometric Method—The microgasometric method of carbon monoxide

estimation in blood was first described by Scholander (1942). Since that time it has undergone many modifications, which have contributed greatly to its improvement and modifications.

The apparatus consists of a narrow 1 cc. syringe with a capillary tube sealed to its nozzle. A detachable rubber cup fits on the top of the apparatus.

The principle of this method is the extraction of the oxygen, carbon monoxide, and nitrogen of the blood by an excess of carbon dioxide evolved by the reagents. The carbon dioxide and oxygen are subsequently absorbed together by alkaline pyrogallol. The volume of the residual gas is measured in the capillary of the instrument before and after the absorption of carbon monoxide by Winkler's solution.

Pyrotannic Method—The pyrotannic method depends on the colorimetric change in blood after the addition of a mixture of pyrogallic and tannic acids. Comparison of the resultant color with a set of standard colors gives an indication of the amount of carbon monoxide present in the blood sample.

Spectroscopic Method—Since the color reactions and the absorption spectrum of carboxyhemoglobin are characteristic, the spectroscopic analysis of the blood gives an approximate indication of its concentration. When more accurate results are required, a Hartridge reversion spectroscope may be employed. However, the accuracy obtained is no better than that of the other procedures requiring less elaborate and less expensive apparatus.

Treatment

The treatment of acute carbon monoxide poisoning is directed toward shortening the period of anoxemia by hastening the elimination of carbon monoxide from the blood. The use of carbon dioxide has been suggested for this purpose by Henderson and Haggard (1922) who demonstrated the efficiency of carbon dioxide and oxygen mixtures by experimental work on dogs and later in a series of human poisoning cases.

Various additional forms of treatment have been prescribed, as, blood transfusion, bleeding, injection of methylene blue. Most of these are now considered incompetent, and many detrimental. For example, methylene blue was proposed because of its stimulating action on the oxygen consumption of the tissues. Later it was pointed out that it enhanced the degree of anoxemia by converting hemoglobin to methemoglobin which has a much greater affinity for carbon monoxide.

The administration of oxygen and carbon dioxide is now the accepted method of resuscitation for acute carbon monoxide poisoning. Artificial respiration may also be necessary initially. The less the patient is disturbed by other forms of treatment, the greater are his chances of recovery. The only effective treatment of chronic carbon monoxide anoxemia, is to eliminate the source of carbon monoxide contamination.

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Feature

C. L. Rogers, Editor

TOAST TO THE CLASS OF 1946

Delivered at the Graduation Banquet by Professor W. A. Scott

I look with envy upon those men like Professor Boyd and Dean Gallie who, knowing that they must soon make a speech, can, nevertheless, eat and enjoy a good dinner. I envy them because it is so different with me. My hands become cold and my head hot; my mouth is dry, and my taste buds dead; the gastric juices retire like monks to their cells; peristalsis ceases, and food lies like a clod in the stomach. But depression of one physiological function is accompanied by stimulation of another. My body apparently becomes resolved to dehydrate itself. This makes me uncomfortable. My brow is bathed in cold perspiration. Knowing these phenomena from experience, I am not only unable to eat, but also must refuse myself the solace of alcoholic stimulation. So I stand before you tonight, hungry, thirsty, cold sober, and frightened. You have your revenge for any discomfort you may have undergone in your oral examination before me.

I wish I could amuse you, but, although not lacking a sense of humour, I have not the gift of being humourous. This faculty is possessed by few and I am not numbered among them, so I must speak in a more prosaic manner. I hope I may interest if not amuse you.

It is my task to give the address to the graduating class—a class distinguished by its erudition, brilliancy, and perspicacity—characteristics not exhibited, I may say, by its choice of a speaker for this dinner. You are just completing your basic training in medicine, and are well aware of the future course you should pursue if you wish to excel in your profession. I do not propose to reiterate what you have read and been told on many occasions about medical reading, hospital training, and hard work. I wish, rather, to talk about another aspect of your future.

The political, social, and economic framework within which you will live will be determined by the men and women of your own generation. You, collectively, will be responsible for it. The form that your world will take I can not predict, but one thing I know. Whatever social and economic changes may come, they will always require your services, which will be valued and rewarded if faithfully performed. It would appear probable that the large emoluments that were formerly possible to those who achieve popular esteem will disappear. Indeed, the government is seeing to it that they disappear into Mr. Ilsley's coffers today. On the other hand, adequate medical attention will almost certainly be brought to a great mass of people to whom it was either denied or obtained by great sacrifice in the past. More physicians than ever will be required, and, as the large incomes of a small group of these physicians disappear, the economic security of the whole profession, especially during periods of illness and old age, will probably be more certain. Your livelihood, therefore, is well assured, and within your generation a greater amount

of leisure will be yours than was the case with your predecessors. The wise employment of that leisure will become of paramount importance.

Material things are important, but they are only a small part of this business of living. You and your fellows can determine the structure of your material world, but only the individual can provide for his immaterial needs, and only too often these are completely neglected.

The intellectual life, the life of the spirit and of the emotions is set for each by himself. The study and practice of medicine, to those who have an aptitude for it, is entrancing, but life offers so many and so diverse pleasures that it should not be spent in the exclusive field of one activity. We pass this way but once, and the enjoyment we miss today will never again present itself. So I counsel you to develop other interests than your profession. I shall speak principally about one, but there are others to which I shall refer briefly.

Example is better than precept, and you have only to look among your teachers to see the extra-professional interests they have cultivated. May I bring a few to your attention. Dr. Van Wyck, for instance, the staid and dignified obstetrician. How many of you are aware that he is a great bridge expert to whom an end play or a Vienna coup is a greater thrill than a successful breech delivery? Or Dr. Walter Campbell, the mountain climber, who fully enjoys life only when leaping like a chamois from crag to crag. Dr. Duncan Graham, the great golfer, with his masterly drives and deadly putts. If you would see the flood-gates of reticence open and a torrent of eloquence pour forth, get Professor Graham to talk about one of his crucial golf matches. His natural garrulousness is greatly increased. Dr. Hepburn, the dour Scot, who might easily be imagined as interested only in a cardiograph, but who neglects his practice to, of all things, shoot ducks. Dr. Boyd, that lover of all good things in life, who foregoes the amenities and comforts of civilization to travel in the wilds of the hinterland looking for new trout streams. And Dr. Gallie, Professor of Surgery, Dean of the Faculty, President of this and Chairman of that, a man so busy that he has a dictaphone in his office and two in his home, yet, in spite of his multitudinous duties he spends many hours a week in his fanatical devotion to the mysteries of stamp collecting. I may be slightly confused in assigning these various interests, but the principle is true. All these men have extra-professional hobbies that enrich their lives. And all these interests have one thing in common—they have a literature—a literature of technique and a literature of contemplation. It is probable that the pleasure derived from this literature is as great as from participation in the hobbies. So, for a few minutes I wish to speak to you about reading, and not about professional reading, which is taken for granted. Dr. Osler one time remarked that it was surprising with what little reading a man could practice medicine, and it was also surprising how poorly he could practice it. I wish to commend to you reading in fields other than that of your life's work. As I am commending such reading I should justify it with some reasons. The first of these is to enlarge our intellectual horizon. Life presents so many interests and pleasurable emotions that none of us can personally experience them all, but we can vicariously partake of them by means of others' experiences

as set down in books. Furthermore, these experiences that we have enjoyed can be recalled even more vividly by the skill of a great writer than by our own memories. John Masefield speaks of the 'golden instances' of his life. Even the most sluggish of us have them, but, lacking expression, they remain undescribed and indefinite. Perhaps we have stood on the shore of a great lake and seen the first pink glow of morning change to the golden streaks of fire as the sun rises in all his glory. Perhaps we have seen the green billows of a previous day's storm roll in on the beach and make the only sound except the song of the newly awakened birds. It may be that we have paddled a canoe at dusk to the shore and smelled the smoke of a birch campfire. We have heard the wild cry of the loon in the north country and felt the salt spray on our faces at the sea, but remain inarticulate without the knowledge of words. The more articulate we become, the more vivid and lasting are these things, and knowledge of words comes with reading and writing.

Taste and discrimination are cultured virtues, not natural qualities. The fastidiousness of our tastes depends upon the efforts we make to cultivate them. With finer appreciations we do not necessarily lose our pleasures in the second best. Apart from the inheritance of a good ear, the appreciation of the sublime masterpieces of music depends upon the intellectual effort of attuning our spirits to them, but to those who achieve the task of making the great symphonies of Beethoven part of their spiritual life, the lesser pleasures of the Strauss waltzes and Gilbert and Sullivan operas still remain. It is equally true of literature. Every feeling and mood of all great writing will never appeal to all of us; it is too diverse; but we can know our individual capacities only by experimenting. We should at least expose ourselves to the best to see if it takes. Who would not welcome the opportunity of spending a week of intimate companionship with Keats? What an experience a long conversation with Carlyle, Plato, or George Bernard Shaw would be! Yet the spirits of all these men lie within our reach if we would seek them, and from acquaintanceship with these choice spirits our discrimination must become finer.

There are, to any of us, only a few persons in the flesh whom we can really call friends and feel that we know them intimately. Fictitious characters of literature more readily lend themselves to our friendship than do real persons as revealed in their biographies. However much he may strive to overcome it, the biographer is always biased, and the portrait, whether of himself or another, reveals that bias. Biography, therefore, may inspire or amuse us, but seldom do we emerge from such a book with a feeling that we have made a new friend. No one can really know Napoleon, nor can we make friends of Frederick the Great or Cromwell. Even Dr. Johnson does not emerge from Boswell's great life as a friend—which is not to decry the great pleasures of that book. In the creation of a fictitious character, however, the author's imagination may roam as it pleases, and the result is often a person more real than one in the flesh. Mr. Pickwick, Parson Adams in Fielding's "David Andrews," Uncle Toby in "Tristram Shandy," and the immortal D'Artagnan are people whom we know and love, and can call our friends. We feel that Mr. Pickwick and his friends not only live today, but they are so real that we could climb on the stagecoach with them and join in their travels.

The knowledge of a person as obtained from letters or diaries probably stands about midway between biography and the persons of fiction. Gertrude Bell emerges from her letters as one of the great women of the world, but she is not of us, nor can we know her intimately. The character of Robert Louis Stevenson revealed in his letters calls forth our love, but from the very fact that he lived we are debarred from calling him a friend. T. E. Lawrence emerges from "The Seven Pillars of Wisdom" and his letters as a personality unique and powerful, yet hardly understandable. Possibly the diary of Mr. Pepys brings him closer than anyone else to the intimacy we feel with fictional characters.

I have indicated a few reasons why we should read. May I now, in a general way, say something about what we should read? I might commence by suggesting what we should not read. Art is long and time is fleeting, and some discrimination must be made. For the most part, we are hurried faster than we can well travel, and the farther we go the faster becomes the pace. There is no leisure in the city, and our "day is ordered by an inscrutable power which drives us to our task". That great favourite of mine, David Grayson, has put it that we cannot look up or down, but only ahead, to that vague success which we love to glorify. There should be leisure, at least in our reading. The modern press spews out such a torrent of new books that it is difficult to know what is worthy of our interest. We should not be concerned, for the problem has been solved. There is a great accumulation of literature that time has certified as valuable, and the judgment of the past is usually valid. I believe you will miss little if you read nothing in the non-professional field that has not retained a solid appeal after a period of at least ten years. Instead of trying to keep up with the mass of recent literature, become familiar with the masterpieces of the past. Hendrick van Loon, whose writings are such a delight, say, "There are, when we come to think of it, only a mere handful of books that have really influenced the human race at large and one of these is hardly twenty pages long." I refer to the poem of Omar the Tentmaker, son of Nishapar—for, "although Omar was entirely negative in describing the joys of the hereafter, he was completely positive in enumerating the less doubtful joys of the here and now." I would not suggest that all of your reading should be among the masterpieces, and I believe that there is a kernel of truth in the observation of that amusing iconoclast, George G. Nathan, who says, "I am always skeptical of the honesty of a man's culture if his library shelves fail to reveal at least a few grotesquely unintelligible volumes. In the heart of every genuinely cultivated man there is a peculiar fondness for certain books that, though perhaps trashy and empty to some of us, are for some reason or other close to his secret fancy." Although, as I say, there may be a kernel of truth in this, it should not be expanded disproportionately.

Do not confine your reading to factual works on the one hand nor to a simple story, however interesting, on the other. Some factual reading is necessary, and and factual reading is not easy. Ernest Raymont in his little book, "Through Literature of Life" says, if we read only for delight and avoid the difficult writers we know the extraordinary sense of joy, exhilaration, and enlargement which

comes when we have read the last words of a difficult book that we have conquered."

Anatole France, great cynic as he was, said, "The pursuit of knowledge is an adventure of the soul." A sense of values can be based only on factual knowledge, and he who has a sense of values can not be a Philistine. He will value art and thought and knowledge for their own sakes, not for their possible utility. Clive Bell in his essay entitled "Civilization" says that the specialist is never completely civilized, and we must remember that the practitioner of medicine is a specialist. He becomes more completely civilized only as his intellectual interests expand. The hope of the world in these perilous times is clear thinking. The skilled politician does not like logic. Lord Baldwin knew political expediency, and has stated that "Politicians must be more interested in persuasion than in proof." But he who thinks logically is difficult to persuade without proof, and logical thinking is the hallmark of the cultured man. It is developed in the very highest degree by factual reading.

I suppose that historical reading might well be included under the previous heading, but it is somewhat different. The future should not be shackled by the traditions of the past, but a knowledge of the past does point the clearest way to the solution of the problems of the future. The man versed in history, obtained by critical reading of the great historians, is a man without intolerance. He is neither a crusader nor a fanatic. He is that highest product of human development —the reasonable man. History has a utilitarian value in human affairs, but, also, the great historical writers give a sense of aesthetic pleasure in their reading. Gibbon is a delight if for no other reason than his superb command of the English language, if there were no thought at all of his scholarship. The same delight is found in Carlyle, Macaulay, and the ancient historical writers. Herodotus, whom I can read only in translation, has always been a great pleasure to me. Could I read him in the original that pleasure would probably be increased.

The greatest intellectual delight that the man of scientific training can have is the cultivation of the literature of the emotions and an appreciation of the beautiful. That delightful modern writer, Lin Yutang, is of the opinion that 'the world has too many cold-hearted people; if sterilization of the unfit should be carried out as a state policy, it should begin with the sterilization of the morally insensible, the artistically stale, the heavy of heart, the ruthlessly successful, the cold-heartedly determined, and all those people who have lost the sense of fun in life.' Our training has taught us to put aside all emotion and personal feeling in our scientific thinking. This is essential to our professional work, but this principle should not be carried into all our life. He has only partially lived who has never been enveloped in great emotion—unscientific, unanalyzed, only felt. In the words of Yeats, "All would be well could we but give us wholly to the dreams—for it is dreams that lift us to the flowing, changing, world that the heart longs for." Science is always partially wrong, for it is always changing as it advances, but the things that were felt and put into words by Homer, Shakespeare, and Shelley, will never change. The great Einstein is surely a scientist, but believes that 'the most beautiful thing we can experience is the mysterious. It is the source of all true art and science.

He to whom this emotion is a stranger, he who can no longer pause to wonder and stand rapt in awe, is as good as dead. His eyes are closed." And Somerset Maugham, who was trained as a doctor, says, "Mysticism is beyond proof and demands no more than an indwelling conviction." Let your reading, therefore, be designed to stimulate your emotional lives and to give you the love of beauty. "The practical man is not apt for fine distinctions and yet in these distinctions truth and the highest culture greatly find their account." (Matthew Arnold) Pre-eminent in this class of literature is all poetry—dramatic, lyrical and descriptive—but it also includes prose—drama, fantasies, and the great imaginative novels.

Lastly, your reading should be designed to develop some familiarity with contemplative thought. A well-rounded intellectural life postulates some knowledge of the philosophic thought of the past. From it stems the theory of all politics, much of religion, and a great many of our ideas of human relationships. The classicists, of course, tell us that we need not go beyond Plato and Aristotle, but few of us are classical students and we should have some familiarity with Hume, Locke, Descartes, and John Stuart Mill, even if we neglect the more modern philosophers. At the installation of our new President a few days ago much was said about the function of a university in promoting the study of human relationships. It is probably the most important problem confronting the world today. The situation is too critical to admit of shallow thinking, and sound thinking can be based only upon some knowledge of the contemplative thought of the past.

I did not intend to go beyond a few general observations about the character of non-professional reading, but I think I will be rash and make some particular suggestions. Years ago an amusing correspondence was carried on in the pages of a sporting periodical regarding what three trout flies a man would take were he confined to that number. A more vigorous discussion would result from trying to choose a specific number of volumes of general literature. Suppose we could have only two novels, two volumes of history, two poems and two plays for the rest of our lives. What would we choose? My choice would probably not be that of any other person here tonight, but I shall be bold enough to give it. The first novel would be "Moby Dick" by Herman Melville, and the second "Tristram Shandy" by Laurence Sterne, and neither is a love story. The history would be Carlyle's "French Revolution" and H. A. L. Fisher's "History of Europe." The poems would be a good translation of Virgil's "Æneid" and Milton's "Paradise Lost", and the plays would be "The Tempest" and "Hamlet." If I could add one philosophical work it would be Locke's "Essay concerning Human Understanding." This is nine volumes. If I could have only one it would be the Bible.

This has been a somewhat lengthy address for a festive occasion such as this. I have given it because extra-professional reading has meant so much to me personally, and I hoped that some flagging interest might be stimulated. That may be unnecessary in the present instance, because, as I remarked before, the class of 1946 is so exceptional in its intellectual attainments that probably I have been carrying coals to Newcastle, and this stimulation was not necessary. I ask you, therefore, members of the Faculty, to drink a toast to the graduating class in Medicine of the University of Toronto of the year 1946.

Abstracts

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MEDICINE I

TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN: REPORT OF CASES TREATED WITHOUT ANTICOAGULANT AGENTS. J. R. Poerner, M.D.; A. J. Geizer, M.D.; F. C. Blake, M.D., F.A.C.P. Annals of Internal Medicine. October, 1945.

THE authors present an interesting report of 20 pages in which they outline their treatment of twelve patients with subacute bacterial endocarditis by massive doses of penicillin over a prolonged period. Eleven of the patients treated were alive and well at the time of writing and in several cases more than a year had elapsed since termination of therapy.

The cases presented and discussed in this article were chosen on the basis that they showed the clinical syndrome of bacterial endocarditis and several positive blood cultures of streptococcus viridans were obtained from each.

The basic plan of therapy was to treat each patient with about 240,000 units of penicillin daily for three to four weeks. Total dosages varied from 5,000,000 to 17,000,000 units, averaging 8,500,000 units. Length of treatment varied from 20 to 70 days, averaging 35 days.

The method of administration which seemed most satisfactory both for the patient's comfort and for therapeutic results was that of slow continuous intravenous infusion maintained day and night. The daily quantity of penicillin was dissolved in not more than 1,500 c.c. of physiological saline or 5% glucose solution. Another method of administration also used with satisfactory results was that of intramuscular injections of 20,000 units at two-hour intervals.

J. W. H.

MEDICINE II

THE HUMAN REQUIREMENTS OF THIAMINE. E. G. Young. C.M.A.J. December, 1945.

BY examination of the results of a dietary survey in 1939-40, Young finds that thiamine requirements are much lower than those proposed by the Canadian Council on Nutrition. The group consisted of 385 individuals in 82 families with an average income of $1,023. The mean intake was found to be .54 mgm. for men and .39 mgm. for women, per day; both these are well below the standard of 1.5 mgm. daily, set by the Council. Because the function of thiamine is related to carbohydrate metabolism, the thiamine requirement varies with the non-fat caloric value of the diet. In the same group it was found that the intake was about .21 mgm.

per 1,000 calories and .36 mgm. per 1,000 non-fat calories; both figures are again much below the standard. Yet there were no cases of clinical polyneuritis in the whole group. Young concludes that while the figures cited may not be optimal, they indicate that the minimal requirements set by the Council are too high.

N. K.

PAEDIATRICS I

ANAEMIAS OF THE NEW-BORN. G. B. Wiswell, M.D., Canadian Medical Journal. December, 1945.

ANAEMIA of the new-born is not common but when it occurs it calls for immediate recognition and treatment. It is a symptom and it indicates an underlying disease. In this article it is associated with four conditions: haemorrhage, infection, prematurity and hemolysis.

1. Anaemia due to haemorrhage occurs most commonly in haemorrhagic disease of the new-born. Rarely it occurs with haemophilia where it is associated with unusual stability of the platelets.

Hypoprothrombinaemia causes haemorrhage of the oozing type, and is spontaneous. Trauma may initiate it and cause death in the first twenty-four hours. Haemorrhage between the second and eighth day is almost always due to hypoprothrombinaemia alone.

2. Anaemia of infection is caused by the more severe infections such as severe pyogenic infections and septicaemia. Milder infections usually do not give rise to anaemia.

Congenital syphilis must always be considered as a cause, whereas tuberculosis is rarely an etiological factor.

Anaemia lowers resistance to infection and infection aggravates the anaemia.

3. Anaemia of prematurity begins soon after birth, reaches its maximum at about eight weeks, and begins to decline at about three months. It is not prevented by the giving of iron to the mother or infant.

4. Anaemia due to hemolysis occurs as a result of an Rh-negative mother bearing an Rh-positive child. Haemolysis only occurs in 2.5 per cent of these combinations and when present leads to excessive regeneration of erythrocytes. Clinically the erythroblastosis occurs in three forms: Haemolytic anaemia, icterus gravis, and congenital hydrops, in ascending order of severity. Haemolysis leads to haemolytic anaemia—the mildest form.

When this progresses, the resulting anoxia causes liver damage which leads to icterus.

When carried further, erythropoiesis takes place in the liver causing pressure atrophy, circulatory disturbances, and hypoproteinaemia. Endothelial damage because of the anoxia, in combination with these three factors leads to oedema. Hence hydrops is the most serious manifestation of the disease with icterus gravis in the middle position and haemolytic anaemia the mildest.

Congenital hemolytic icterus, mediterranean anemia, Lederer's anemia, pur-

pura, haemophilia and leukemia are rare in the new-born and fairly easily distinguished from erythroblastosis.

The remainder of the article deals with differential diagnosis, prognosis and treatment of all the anaemias. A table is included on the differential diagnosis of anaemias in live born infants.

L. R.

PAEDIATRICS II

THE THREE CLINICAL PICTURES OF ERYTHROBLASTOSIS FETALIS FROM "ERYTHROBLASTOSIS FETALIS". Journal of Paediatrics. October, 1945.

ERYTHROBLASTOSIS fetalis is the broad clinical picture including the clinical entities (1) anemia of the new-born, (2) icterus gravis neonatorum, (3) hydrops fetalis.

Anemia of the new-born: Characteristic is whiteness of skin and mucosae, obscured by jaundice at birth, but seen on recession of the icterus. The infants are weak and liver or spleen enlargement occurs. Diagnosis is by clinical signs and the anemic blood picture. Prognosis is good, but the course may be prolonged. Anemia may be stationary or even aggravated until the sixth week, when the young erythrocyte count becomes normal. Four months may be required for the hemoglobin and erythrocyte increase to return to normal.

Icterus gravis neonatorum: Jaundice is the prominent symptom appearing either at birth or in twenty-four to forty-eight hours. A golden vernix caseosa arouses suspicion. The infants are weak. The disease progresses to stupor and convulsions. In the terminal stages, vomiting, dyspnea, cyanosis, and frothing of blood-stained fluid are frequent, cutaneous hemorrhage is not uncommon. Liver and spleen are palpable. Pregnancy associated with icterus gravis shows a greater incidence of toxemia. Jaundice, large liver and spleen, and increased nucleated erythrocytes form a diagnostic triad. Icterus gravis should be anticipated in a mother with a history of repeated stillbirths without apparent cause, or of erythroblastosis.

Hydrops fetalis: A stillborn infant or death of the child after feeble respiration occurring up to six days is the rule. The infant has a waxy skin, multiple cutaneous hemorrhages, universal edema, swollen face, short neck, and distended abdomen and enlargement of liver and spleen. Diagnosis at birth is by appearance of the infant. Amber amniotic fluid directs suspicion. Intrauterine diagnosis by X-rays shows thickened, dense subcutaneous tissue, and a corona surrounding the skull bones, due to scalp edema.

These three conditions are related, differing only in severity, the mildest is congenital anemia, with spontaneous recovery. In icterus gravis, recovery is about seventy-five per cent. The severe hydrops fetalis is fatal.

M. L. B.

PSYCHIATRY I

PSYCHIATRY IN INDUSTRY. D. E. Cameron. C.M.A.J. December, 1945.

THE role of psychiatry in industry is threefold—teaching, clinical practice, and research.

Teaching: Foremen and managerial personnel must be taught the basic explanations of man's behaviour—the meaning of fear, leadership, frustration, etc., and their relation to jobs. The industrial doctors are badly in need of learning the large part that psychological factors play in illness. It is known that certain jobs are dangerous to certain types of individuals—e.g. repeated repetition to the tense high-strung person. It is psychologically risky for certain types of personalities to work together. Doctors must learn the psychosomatic nature of illness generally as well as the importance of psychogenic factors.

Clinical Practice: Doctors should, while examining new employees, learn those who lack good mental health, in order to advise satisfactory placement. He must be prepared to help those who seek interviews; of these, there are two large groups—those developing tension or frustration due to their jobs, and those having trouble with personal relations.

Research: Much work can yet be done in recognizing the jobs which are psychologically dangerous, and in the selection of personnel by ability and personality. The problem of tension due to speed-up industry is particularly outstanding, and we must learn what sort of people and what type of job produce it.

N. K.

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* Gold et al., J. Pharmacol. 82:187, 1944.

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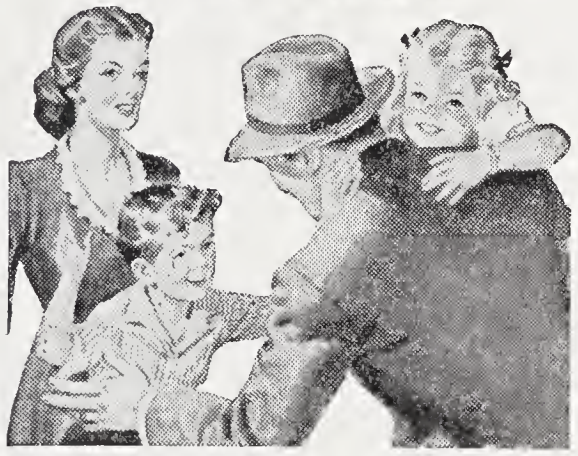

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EVERY CASE OF SYPHILIS MUST HAVE AN EXAMINATION OF THE CEREBRO-SPINAL FLUID

Cases of early Syphilis, treated according to a schedule requiring six months or longer, should have a lumbar puncture at the conclusion of treatment.

Cases of early Syphilis, treated with a rapid form of treatment, should have a lumbar puncture six to nine months from the time treatment was begun.

Cases of latent Syphilis, or of late forms of Syphilis, should have a lumbar puncture **immediately**, before beginning treatment.

CO-OPERATION OF PATIENT

A lumbar puncture is to be considered as a minor surgical intervention and, like all surgical interventions, should **not** be performed **without** the consent of the patient.

As a rule, by exercising a certain amount of tact, and by giving appropriate explanation to the patient, there is no difficulty in obtaining his consent.

When, in spite of all explanations given, the patient refuses to submit to a lumbar puncture the physician **cannot** consider himself as released of further responsibility in this regard. He should inform the patient that his treatment cannot be considered as complete unless the examination of the cerebrospinal fluid is negative, that the cerebrospinal fluid which has not been examined cannot be presumed to be negative, and that, therefore, further treatment will have to be given. At each subsequent treatment, the physician should try to gain the confidence of the patient. After a time, he may explain more fully to him the necessity for a cerebrospinal fluid examination. It is very rare that after a few weeks of such additional treatment and discussion of his problem the patient does not give his consent to a lumbar puncture.

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It Can Happen Here

Example of severe rickets in a sunny clime.

LEST WE FORGET—we who are of the vitamin D era—severe rickets is not yet eradicated, and moderate and mild rickets are still prevalent. Here is a white child, supposedly well fed, if judged by weight alone, a farm child apparently living out of doors a good deal. This boy was reared in a section having a latitude between 37° and 42°, where the average amount of fall and winter sunshine is *greater than that in the major portion of Canada*. And yet such stigmata of rickets as *genu varum* and the quadratic head are plain evidence that rickets does occur under these conditions.

How much more likely, then, that rickets will develop among city-bred children who live under a smokepall for a large part of each year. True, vitamin D is more or less routinely prescribed nowadays for infants. But is the antiricketic routinely administered in the home? Does the child refuse it? Is it given in some unstandardized form, purchased from a false sense of economy because the physician did not specify the kind?

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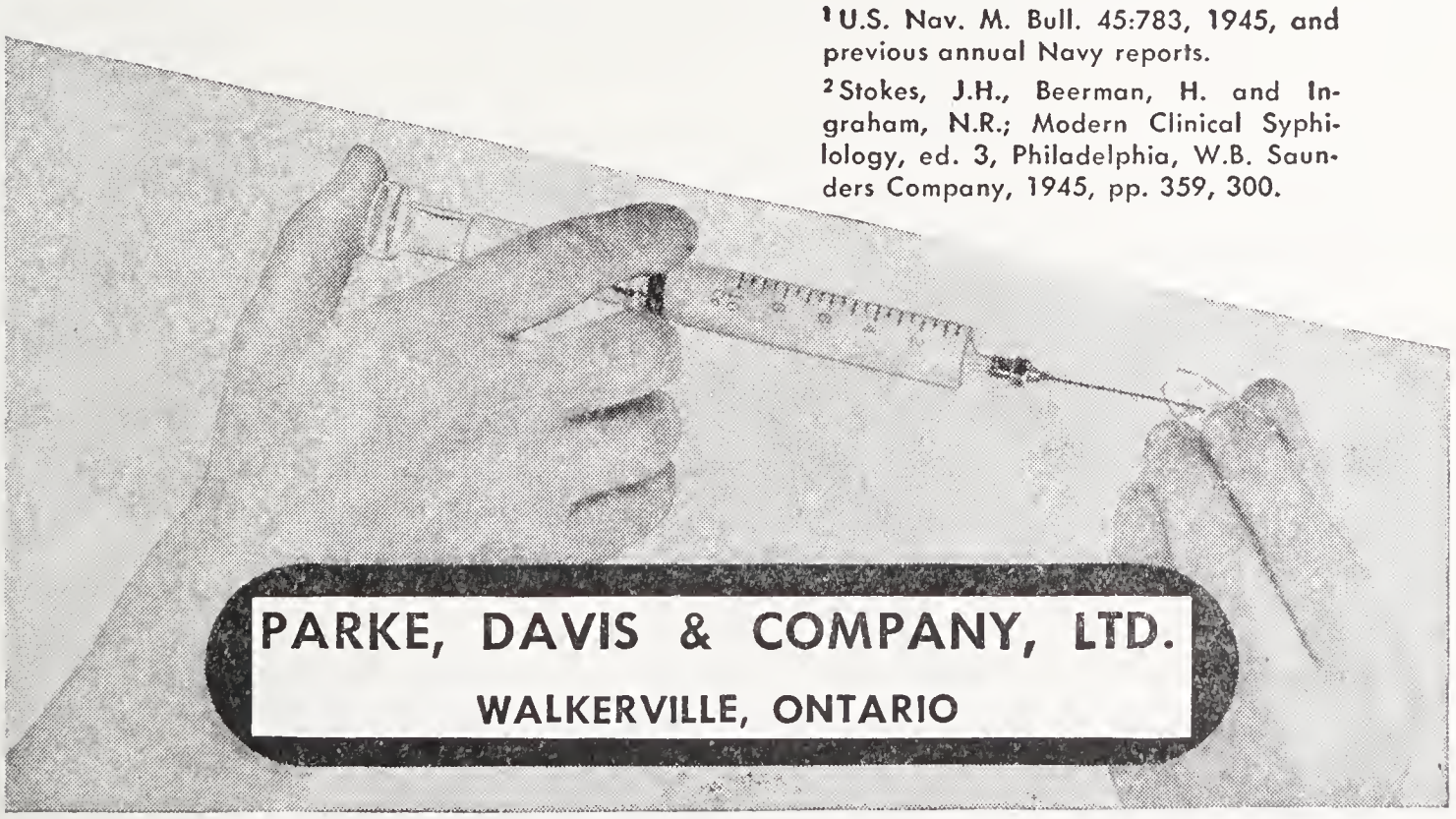
[1] U.S. Nav. M. Bull. 45:783, 1945, and previous annual Navy reports.

[2] Stokes, J.H., Beerman, H. and Ingraham, N.R.; Modern Clinical Syphilology, ed. 3, Philadelphia, W.B. Saunders Company, 1945, pp. 359, 300.



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